SYNTHETIC APPROACHES TO CARBOTRICYCLIC AND HETEROTRICYCLIC NATURAL PRODUCTS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1997

To Francisc Boldea and Maria and Victor Dancaescu, my grandparents, who never doubted this was possible

ACKNOWLEDGMENTS

It is with much gratitude that I acknowledge the guidance of my research director and mentor, Dr. Merle A. Battiste, whose enthusiasm for chemistry and understanding of nature will always inspire me. I am convinced that none of this would have been possible without his patience and unique ability to motivate his students to do better, while making their experience exciting and enjoyable.

Thanks also go to Dr. Eric J. Enholm for the many helpful discussions on specific experimental procedures. I also wish to express my gratitude and appreciation to Dr. W. R. Dolbier Jr. for organizing the Mechanistic Bull Session, probably the best learning environment encountered during graduate school. Acknowledgments also go to Dr. Nigel Richards and Dr. Charles Allen for their time and effort as members of my supervisory committee. Last but not least, thanks go to Dr. James A. Deyrup for all his help and guidance and to Dr. Thomas Hudlicky for offering a unique and fascinating approach to the area of natural product synthesis. I am also grateful to my co-workers, Patricia and Ivani, for their intellectual contributions and friendship, as well as to the departmental scientific support staff, namely Dr. David Powell, Dr. Khalil Abboud and Dr. Ion

Ghiviriga, for all their patience and expertise. This work would definitely not have been possible without all their help. In addition, I would like to thank Gregg Kottas and Michael D. Bartberger for their contributions to this work, as well as my two best friends, Nagraj Bokinkere and Anthony Dribben for the many helpful discussions and support.

Special thanks go to the faculty members at the University of West Florida, namely Dr. R. K. Birdwhistell, Dr. J. E. Gurst, Dr. S. P. Tanner and Dr. G. Chiu, for all their help, encouragement and guidance during a very difficult period of adaptation to a new language and culture.

This acknowledgment would not be complete without acknowledging the two people who steered me towards chemistry at a very young age, Mr. Valeriu Avramescu, my middle school chemistry teacher, and Dr. Maria Borbil, my High School Organic Chemistry professor.

No acknowledgment can express the gratitude I have towards my family, my parents, Lia and Bujor Boldea, and my grandparents, for all the sacrifices they have made for me. I probably owe this accomplishment to my two grandfathers, Francisc Boldea and Victor Dancaescu, for their confidence in me and for never accepting less than my very best effort.

Finally, I wish to acknowledge my best friend, my wife Melania, for her patience, love and understanding during these past five years.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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By

Lucian Boldea

May, 1997

Chairman: Dr. Merle A. Battiste
Major Department: Chemistry

This dissertation investigates the applicability of the intramolecular Diels-Alder reaction to the construction of some tricyclic natural products. Studies regarding substituent effects and thermal rearrangements that accompany the cycloaddition are presented.

The first area of study involves the synthesis of an intermediate required for the construction of Forskolin. Studies using a variety of dienes and dienophiles reveal that under carefully chosen conditions, cycloaddition is a reality, but is followed by a thermal isomerization of an

olefin in the cycloadduct. The structure of the product is then confirmed by X-ray crystallography.

The second area involves the development of methodology for the construction of a new class of heterodienes required in the Diels-Alder synthesis of pyranocoumarins. The study gives new insight into 1,4-reductions of α,β-unsaturated-γ-ketoesters using diisobutylaluminum hydride and lithium aluminum hydride. Under appropriate conditions, 1,4-reduction products have been obtained with both reducing agents. Comparative studies using several olefination methods affording dienes ranging from terminal olefins to ketene- and thioketene acetals are presented.

The third area of study involves polar organic media such as lithium perchlorate in diethyl ether. Our results reveal that allylic alcohols and esters, when treated with a 5M ether solution of lithium perchlorate, in the absence of a nucleophile, afford elimination products under mild conditions. The study also revealed the ability of lithium perchlorate to hydrolize silyl allyl ethers in excellent yields. Studies using chiral alcohols further confirm the existance of a carbocationic intermediate.

CHAPTER 1
INTRODUCTION

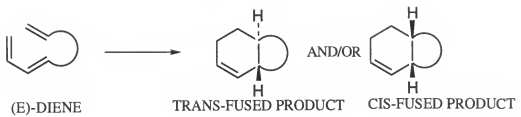
Brief Overview

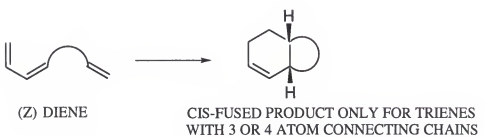
The Diels-Alder reaction, first described in 1928,[1] has enjoyed widespread use in organic synthesis.[2] This type of [4+2] cycloaddition is particularly useful due to its ability to form two carbon-carbon sigma bonds and up to four stereocenters in one single step. Amazingly it took over 25 years from the first reports on the Diels-Alder reaction until the first intramolecular application was reported.[3] Since 1970, the interest in this area has increased dramatically. New methodology has been developed that allows the control of the regiochemistry, as well as, more recently, the absolute stereochemistry, which makes this reaction a very powerful tool in the construction of natural products containing complex polycyclic ring systems.

Based on the point of connection of the diene to the dienophile, two main types of intramolecular Diels-Alder reactions can be identified (Scheme 1-1). Type I reactions involve trienes with the connecting chain attached to the diene terminus, while type II substrates have the dienophile tethered via one of the internal diene positions.

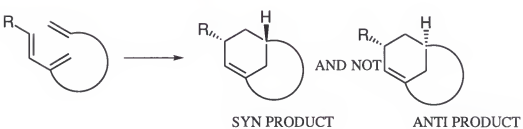
Scheme 1-1

Type I Trienes





Type II Trienes



In order for this reaction to be a useful synthetic method, it is critical to control the regiochemistry, as well as the stereochemistry. The vast majority of type I reactions are feasible only if the connecting chains contain at least three carbon atoms.[4] The fused rather than the bridged product is observed in the majority of examples. The bridged products are only observed in type I reactions if the connecting tether contains ten or more carbon atoms. The stereochemistry of type I reactions is highly dependent on the stereochemistry of the diene. A (Z) diene usually leads to a *cis*-fused system, since the transition to the *trans*-fused system is highly strained. Less stereocontrol can be achieved with (E) dienes, which usually lead to a mixture of *cis* and *trans*-fused systems.[4]

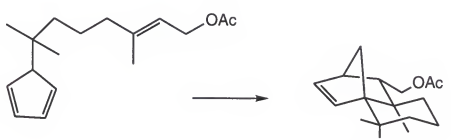
In the case of the type II reactions, diastereoselection is even more challenging, and can usually only be controlled by the strain in the bicyclic system formed. If the connecting tether contains three or four carbon atoms, usually the *syn* adduct is observed as a single product.

Historical Review

The first example of an intramolecular Diels-Alder reaction appears to be an unpublished result by Alder,[5] involving the conversion of 1,4-pentadiene and dimethyl

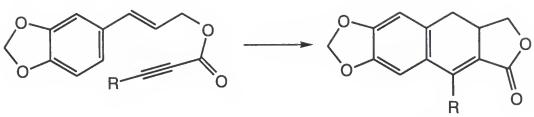
acetylene dicarboxylate into a bicyclo[4.1.0]heptane derivative. The reports immediately following are believed to be incidental in nature[6,7,8]. The first two reports of a deliberate intramolecular [4+2] cycloaddition appeared in 1963. The first report[9] was an attempted synthesis of longifolene **101** (Scheme 1-2), while the other[10] was a synthesis of a podophyllotoxin degradation product, **102** (Scheme 1-3). The reaction mechanism was studied extensively beginning in 1965[11], through studies involving regio- and stereospecific cyclizations of methyl *trans,trans-* and *trans,cis-*2,7,9-decatrienoates resulting in tetrahydroindans **103** and **104** (Scheme 1-4). The formation of regioisomers not favored by the intermolecular reaction was observed. Further, the same authors found that reducing the carbon bridge to two carbon atoms prevents the formation of adducts. An early study in 1967[12] on the intramolecular reactivity of cyclohexadienes proved that strained ring systems could be formed and yielded useful thermodynamic data on the vinylcyclohexadiene-tricyclo[3.2.1.0]oct-3-ene equilibrium.

Scheme 1-2



101

Scheme 1-3



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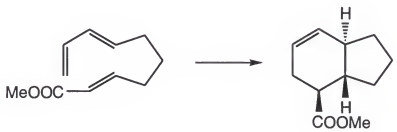
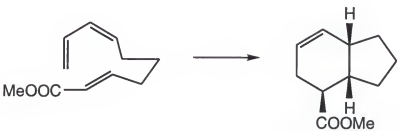
Scheme 1-4



103



104

The major structural types of dienes[12] reported to date are acyclic dienes, endocyclic 5-ring dienes, endocyclic 6-ring dienes, endocyclic dienes in rings >6, and endo,exo dienes, for both aromatic and alicyclic systems, Claisen rearrangement systems, and *o*-quinodimethanes. The present

discussion will be limited to exocyclic dienes generating 6,5, and 6,6 fused ring systems.

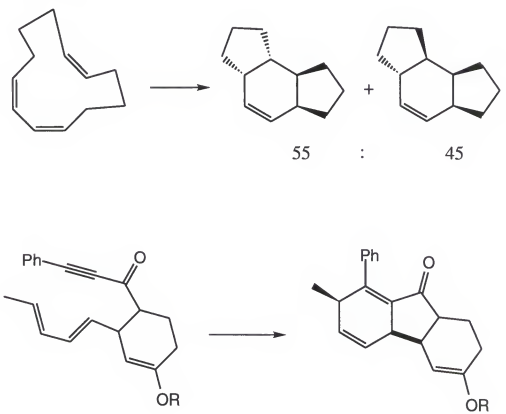
Bicyclo[4.3.0]nonenes

[4.3.0]nonenes are the smallest bicycles which can be prepared by intramolecular Diels-Alder reactions.[13] A study by House and Cronin[14] revealed that the preparation of [4.2.0]octene is not feasible by intramolecular [4+2] cycloaddition and thus the chain connecting the diene and the dienophile must contain three or more atoms, although certain specialized cyclic and bridged cases have shown that this generalization is not valid.[13] The cycloadditions are regiospecific and give fused rather than bridged ring systems. This is mainly attributed to geometrical constraints for short connecting chains and is not influenced by the substitution pattern on the dienophile component. However, in trienes with longer connecting chains, as well as in cyclic dienes, the geometrical constraints can be overridden by other factors. The resulting perhydroindenes are "*meta*-substituted" in contrast to the "*ortho*-substitution' pattern encountered in related intermolecular cases.

Scheme 1-5 contains some relevant examples of related triene systems.[15] The reactions are generally stereoselective. The stereochemistry is established by the orientation of the dienophile as it approaches the diene. The mode of approach is determined by conformational, steric and

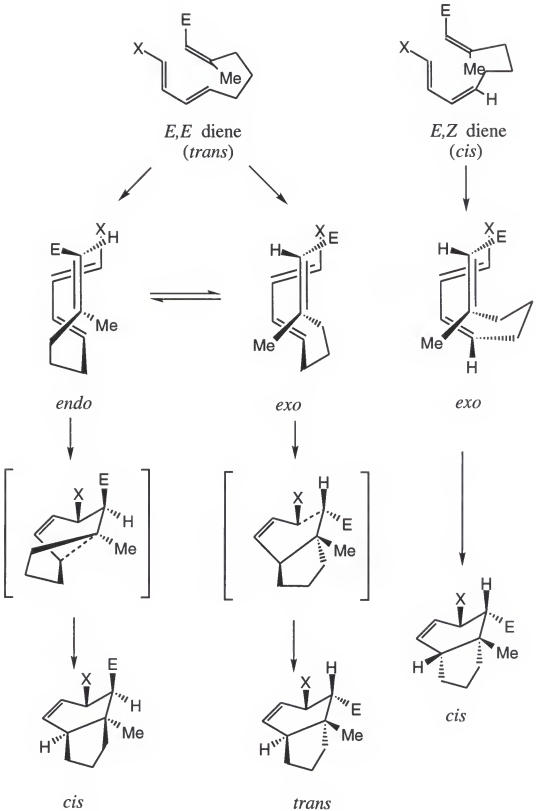
electronic effects which may vary independently. Side chain substituents can also have a great influence on the stereochemical outcome of the reaction. Scheme 1-6 outlines a model case and illustrates some of the subtleties involved.[13]

Scheme 1-5



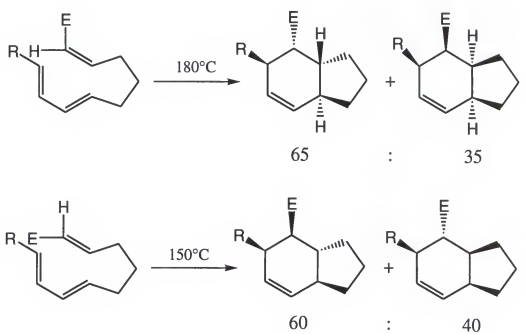
Two modes of approach are available: an *endo*-approach, where the electron withdrawing substituent on the dienophile component overlaps with the diene, and an *exo*-approach, with the electron withdrawing substituent on the dienophile pointing away from the diene.

Scheme 1-6


E
X
Me
E,E diene
(trans)
E
X
Me
H
E,Z diene
(cis)
endo
exo
exo
cis
trans
cis

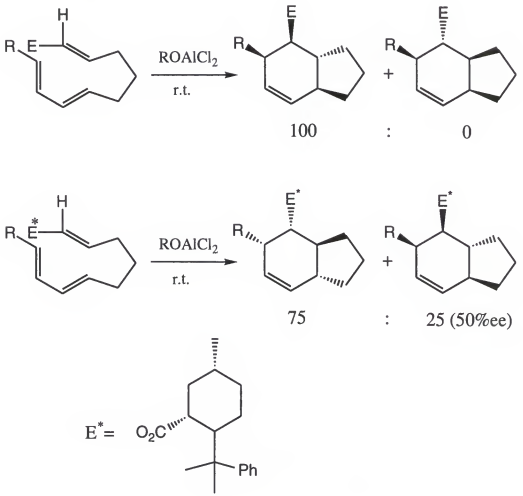
The stereochemistry of the diene component plays an important role in the outcome. As shown in Scheme 1-6, *E,E* dienes can afford both *cis*- and *trans*-fused systems, while *E,Z* dienes afford *cis*-fused products exclusively.[13] In general, steric effects are more important than electronic effects because the bicyclic products are predominantly *trans*. In the case of terminally substituted dienophiles, the outcome is independent of the stereochemistry of the dienophile (Scheme 1-7).[16] Thus in intramolecular Diels-Alder reaction the *endo* rule fails, emphasizing that secondary orbital interactions are not of prime importance.

Scheme 1-7



The use of Lewis acids as catalysts dramatically improves selectivity due primarily to dienophile polarization, and in the case of *trans*-dienophiles produces *trans*-fused adducts exclusively (Scheme 1-8).[16]

Scheme 1-8



This is believed to be primarily due to a combined effect of the preferred *endo* transition state and secondary orbital interactions. In the case of *cis* dienophiles, the two effects are opposed, resulting in poor reaction mixtures.

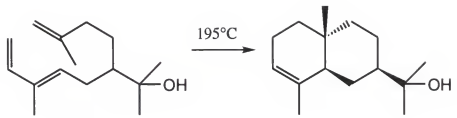
Another limitation of Lewis acid catalysts is their incompatibility with ether oxygen substituents.

In spite of the general failure of the *endo* rule, product distribution can be rationalized using secondary orbital interactions. A popular explanation involves the theory of a non-synchronous transition state.[17] The reaction is still presumed to be concerted, in that all new bonds form concomitantly, but minimization of non-bonded interactions results in an unsymmetric transition state. Bonding occurs preferentially between the termini with the largest LUMO coefficients.

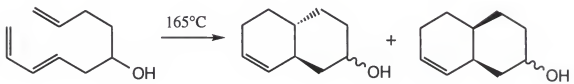
Bicyclo[4.4.0]decenes

The addition of an extra methylene subunit to the connecting chain reduces the geometric constraints on the transition state and therefore permits the formation of both *endo* and *exo* transition states, leading to mixtures of *cis* and *trans* adducts.[13] In the absence of bulky substituents, there is a slight preference for *cis* products. The factors governing the stereochemistry of the transition states involved in the formation of bicyclo[4.4.0]decenes are based on the well established facts that six member rings prefer chair conformations and that substituents prefer equatorial positions. The case of equatorial substituents is evident in Scheme 1-9,[18] comparing the reaction of **105** to the reaction of **106.**

Scheme 1-9



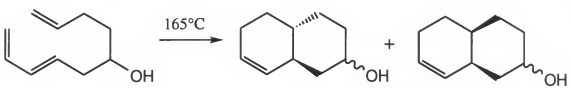
105



106

55 : 45

Scheme 1-10



106

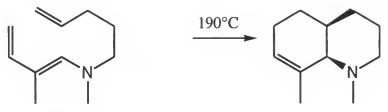
55 : 45

107

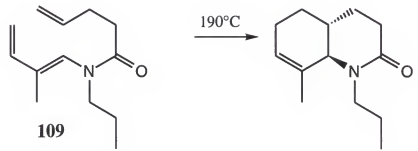
However, as pointed out by the example shown in Scheme 1-10, over generalization can be detrimental when rationalizing the different product distributions from the reaction of **106** and **107**.

Secondary orbital effects are found to play a minor role, unless sidechain ketones are present. Oppolzer[19] first noted the importance of a carbonyl group in the stereochemical control of the intramolecular Diels-Alder reaction. The overlap between the adjacent π systems in the transition state was found to have great bearing on the stereochemistry of the product in the case of amides **108** and **109** (Scheme 1-11). The major products result from the adoption of the conformation in which overlap is most easily retained in the transition state. According to Oppolzer, careful placement of a carbonyl group can allow the preparation of the desired diastereomer, a process known as "carbonyl co-planarity control". If the carbonyl group is in conjugation with the diene, *trans*-products predominate,[20] as shown in Scheme 1-12 by comparing **110** with **111**. The reverse effect can be obtained by replacing the sp^2 hybridized carbon with an sp^3 carbon via the formation of a cyclic acetal (Scheme 1-13).[20]

Scheme 1-11

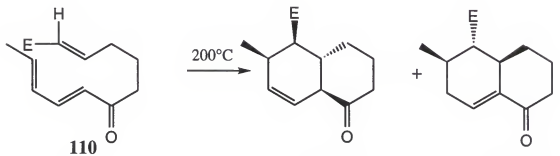


108



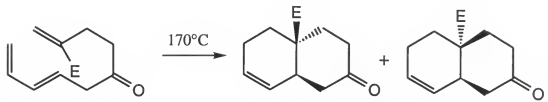
109

Scheme 1-12



110

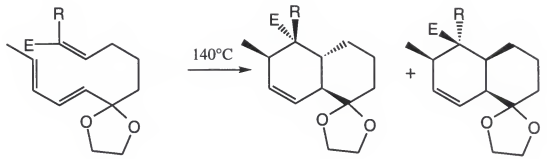
Major Minor



111

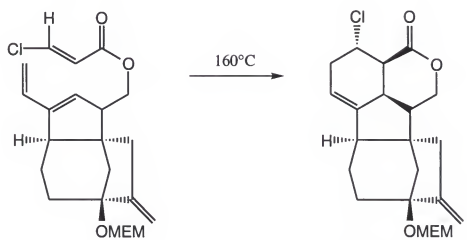
25 : 75

Scheme 1-13



19 : 81

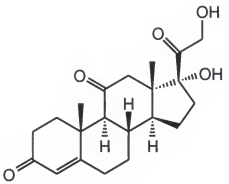
Scheme 1-14



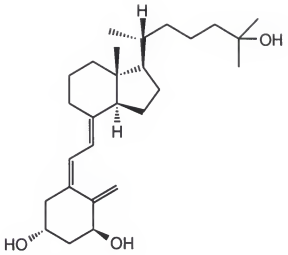
112

The *cis*-fused product predominates in this case, as well as in cases where the sidechain is adjacent to the dienophile, thus encouraging the *endo* transition state. Corey used this observation in the total synthesis of gibberellic acid by preparing a key intermediate **112** (Scheme 1-14).[21]

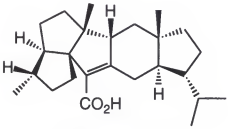
Scheme 1-15



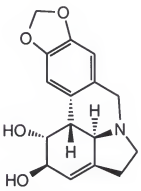
Cortisone



Vitamin D



Retigeranic acid



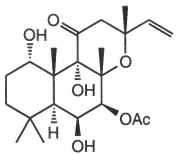
Lycorine

As a result of the widespread occurrence of decalin systems in nature, the intramolecular Diels-Alder reaction has been the key step in the construction of important natural products, a few of which are shown in Scheme 1-15.

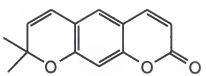
The goal of this study is the application of the intramolecular Diels-Alder reaction to the synthesis of

Forskolin, and the development of a general route to intramolecular Diels-Alder heterotriene systems required for the formation of pyranocoumarins (Scheme 1-16).

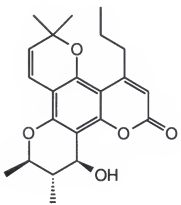
Scheme 1-16



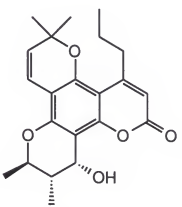
Forskolin



Xanthyletin



Calanolide A



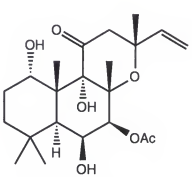
Calanolide B

CHAPTER 2
SYNTHESIS OF A HEXAHYDRO-2*H*-NAPHTO-[1,8-BC]-FURAN-2-ONE PRECURSOR TO FORSKOLIN

Introduction

Forskolin **(1)** was discovered in 1977 by deSouza *et. al.*[22] as part of an effort by Hoechst Pharmaceutical Research toward the discovery of new leads from Indian medicinal plants. It was isolated from the crude methanolic extract of *Coleus forskohlii* and displayed interesting cardioactive properties as a pure compound. Shortly after, numerous research groups embarked on the structural identification and chemical characterization of Forskolin.

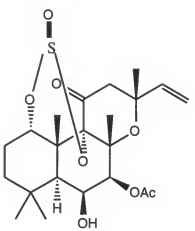
Scheme 2-1



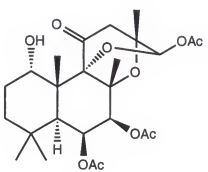
Forskolin (1)

The fact that the molecule could only be monoacetylated and failed to undergo typical ketone tests indicated the hindered nature of the respective oxygen functionalities.[23] The relative configuration of the hydroxyl groups at C-1 and C-9 was established by treatment of **(1)** with thionyl chloride leading to sulfite ester **201**, while the α-configuration of the vinyl group was established by an ozonolysis-acetylation sequence on 1,6-diacetylforskolin resulting in the formation of hemiacetal **202** (Scheme 2-2). ^{1}H NMR and circular dichroism established the *trans*-stereochemistry of the A-B ring junction and the configuration at C-1, α-OH, C-5, α-H, C-6, β-OH, C-9, α-OH, C-10, β-CH_3, C-13, and α-vinyl. The structure was later verified by X-ray crystallography.[24]

Scheme 2-2



201



202

Pharmacologically, forskolin is characterized by potent positive inotropic and blood pressure lowering activity, activities which have been attributed to the activation of adenylate cyclase, a membrane-bound enzyme. Preliminary clinical studies have indicated that forskolin represents a novel drug useful in the treatment of congestive heart failure, bronchial asthma and glaucoma.[25]

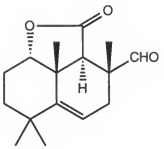
A careful inspection of the structure of forskolin reveals a rather simple framework that accommodates a large number of oxygen functionalities resulting in a number of 1,3 diaxial interactions which present a formidable synthetic challenge. Since the discovery of forskolin a large number of synthetic groups have embarked on the total synthesis of the natural product, and later on the development of efficient routes to key intermediates in the total synthesis.

Despite the large number of published synthetic efforts towards the construction of forskolin, a very small number of synthetic sequences that result in the total synthesis have appeared in the literature.[26] A common feature of the majority of the published synthesis is the use of the intramolecular Diels-Alder reaction as the key step in the construction of the A-B ring system. In all cases ring C was constructed as a final stage in the synthesis.

The Ziegler Approach

In 1985, Ziegler and co-workers[27] reported the synthesis of lactone **210** (Scheme 2-3), a key intermediate.

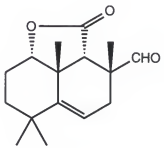
Scheme 2-3



210

Ziegler's approach was centered around the intramolecular Diels-Alder cycloaddition of adduct **209**, prepared by the esterification of alcohol **208** with the corresponding carboxylic acid (Scheme 2-5). Thermolysis of the triene afforded tricyclic lactone **210** with the stereochemistry for an *exo*-cyclization. Ziegler noted that at higher temperatures, the yield of lactone **210** improved.

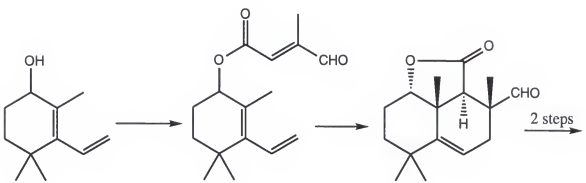
Scheme 2-4



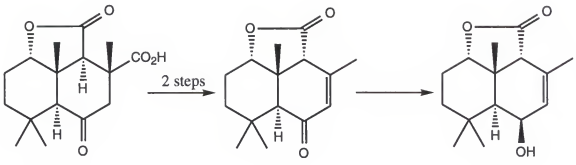
211

However, while at lower temperatures 55 % of the starting material is recovered, at higher temperatures the isomeric lactone **211** (Scheme 2-4) was also produced. This can be attributed to the increased stability of the *cis*-lactone versus the *trans*-lactone. The stereochemistry of the adducts was assigned by X-ray crystallography. With adduct **210** in hand, Ziegler proceeded by hydroboration followed by Jones oxidation to afford keto acid **212** which was equilibrated under basic conditions to the epimeric *cis*-lactone. Subsequent decarboxylation yielded the conjugated ketone **213** which was reduced to the axial allylic alcohol **214** followed by a hydroxyl-directed epoxidation and base catalyzed opening sequence to afford **215**. The synthesis was completed in a subsequent report by Ziegler[28] with the construction of ring C, which is not the subject of our study.

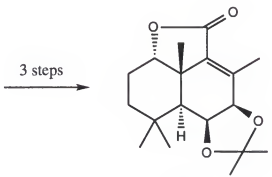
Scheme 2-5



208 **209** **210**



212 **213** **214**

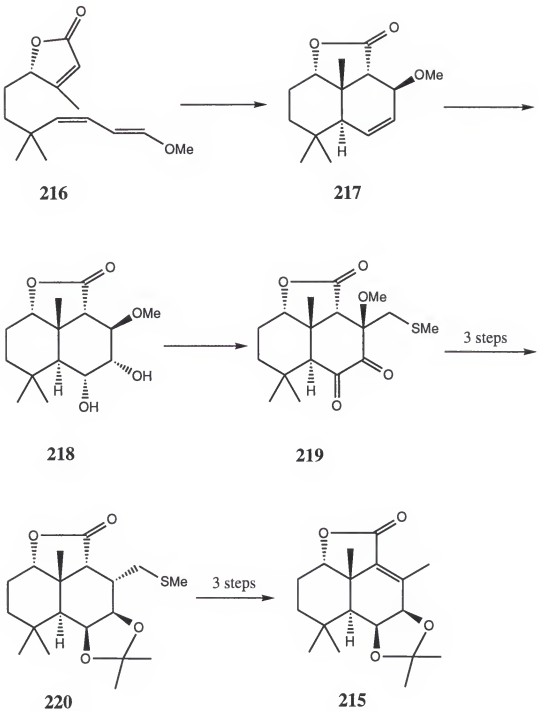


215

The Ikegami Approach

Ikegami and co-workers[29] achieved the second total synthesis of forskolin by using the same key intermediate tricyclic lactone **215** as Ziegler. However, the two sequences are clearly different, especially in the triene selected for the intramolecular cyclization. In his approach, Ziegler started with ring A and constructed ring B via an intramolecular cycloaddition. Ikegami, however, started with the lactone functionality and constructed both rings (A and B) in the cycloaddition step, as illustrated in Scheme 2-6.

Scheme 2-6



216 **217**

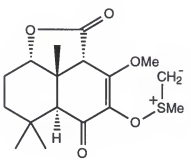
218 **219**

220 **215**

Butenolide **216** was the diene which Ikegami prepared via a 6 step sequence as a mixture of geometric isomers.

Fortunately, under the cycloaddition conditions, the *Z,E*-diene isomerized to the required *E,E*-diene involved in the cyclization affording cycloadduct **217** in good yield. For the introduction of the *cis*-diol unit present in Forskolin, Ikegami attempted to take advantage of the double bond in **219**. However, osmium tetroxide dihydroxylation occurred from the less hindered face affording the wrong stereochemistry for the diol functionality in compound **218**. This problem was corrected in two additional oxidation-reduction steps. One obvious shortcoming of Ikegami's approach was the absence of one of the methyl substituents in ring B. In order to install this group, Ikegami used the Parikh-Moffat reagent which oxidized the diol to the diketone, and subsequently reacted with the C-7 ketone via a [2,3] sigmatropic rearrangement of the sulfur ylide to afford **219**, as shown in Scheme 2-7.

Scheme 2-7



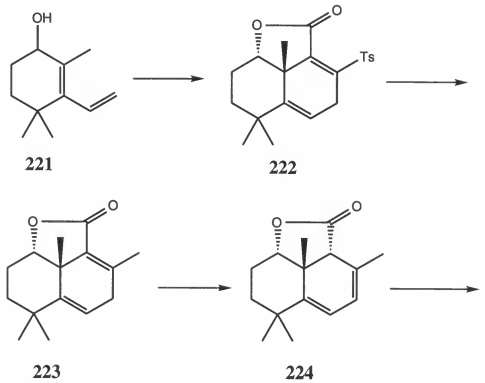
Reductive removal of the methoxy group and stereoselective reduction of the diketone using a bulky

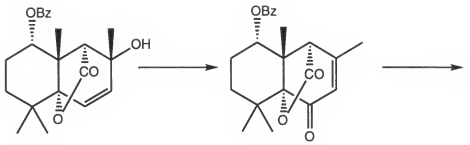
reducing agent finally afforded the desired diol, which was converted into acetonide **220**. The thiomethyl functionality was removed by oxidation and thermolysis of the sulfone. Base-catalyzed isomerization of the exocyclic double bond gave the desired intermediate **215**.

The Corey Approach

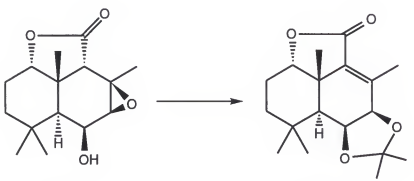
The third total synthesis of forskolin was carried out by Corey and co-workers,[30] who not only used the intramolecular Diels-Alder approach like Ziegler and Ikegami, but also used the same intermediate tricyclic lactone **215** present in the two previous synthesis (Scheme 2-8).

Scheme 2-8





225 226



227 206

Corey's approach relies on the effectiveness of 3-toluenesulfonyl propynoic acid as a dienophile, and reports that alcohol **221**, in the presence of this acid, yields the corresponding intramolecular adduct **222** in excellent yield under very mild conditions. However, Corey's approach has the same shortcoming as Ikegami's, in that it does not install the methyl substituent on ring B, although in Corey's case this installation requires only one additional step to afford **223** using dimethylcuprate. Subsequent isomerization of the cyclohexadiene system under basic conditions to the thermodynamic 1,3 diene affords **224.** Addition of singlet oxygen, followed by reduction and selective benzoylation

yielded **225**. The tertiary alcohol unit then underwent a 1,3-oxidative rearrangement to afford enone **226**. Reductive cleavage of the lactone, followed by esterification with diazomethane and reduction of the unsaturated ketone to the axial allylic alcohol and epoxidation of the double bond afforded intermediate **227**, which was easily converted into tricycle **206**.

Syntheses of Advanced Intermediates

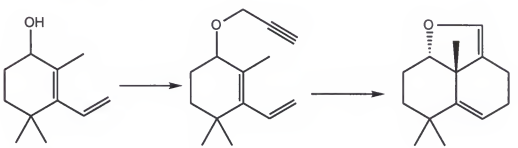
Since the publication of the three total syntheses of forskolin, much effort was devoted to the synthesis of advanced intermediates similar to or identical to the ones used in the three syntheses.

Kanematsu *et al.*[69] reported the synthesis of the Ziegler intermediate **215** by using an allenyl ether as the dienophile in the cyclization. As shown in Scheme 2.9, when propargyl ether **227** is treated with potassium *tert*-butoxide in refluxing *tert*-butanol, adduct **228** was generated via an allenyl ether intermediate.

Wu and co-workers[32] published an alternate Diels-Alder approach completely different from any previously published method. Wu also starts with ring A present in the starting material, but links the dienophile used in the intramolecular cyclization to the opposite end of the diene, generating a linear tricyclic lactone, as shown in Scheme 2-10. Despite the doubly activated dienophile, high temperatures were required for the cyclization. Attempts to carry out the

cyclization in a sealed tube at 150°C resulted in a complex reaction mixture. The cyclization was successfully carried out in refluxing xylenes in the presence of hydroquinone at reaction times of 90 hours. However, the usefulness of Wu's intermediate in the total synthesis of Forskolin still remains to be proven.

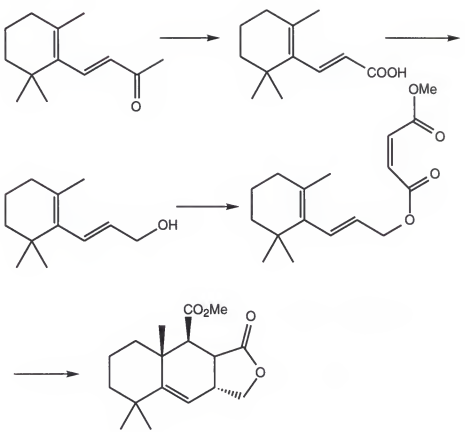
Scheme 2-9



221 **228** **229**

Prange and co-workers[33] reported a novel approach to solving one of the key problems in the total synthesis, the oxygenation at C-6 and C-7. Their approach was based on the 1,4-dioxene derivative **230** shown in Scheme 2-11. As with previous synthesis, Prange's approach also affords Ziegler's intermediate, but has obvious advantages over Ziegler's original approach.

Scheme 2-10

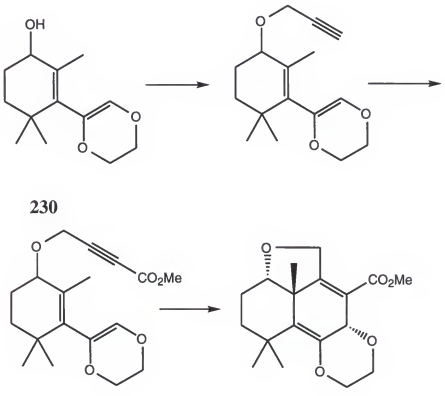


The most recent total synthesis of Forskolin was published by Lett and co-workers[34] in 1996. The originality of the approach lies in the construction of ring C, as well as in the oxygenation of ring B. However, the key step, the intramolecular Diels-Alder reaction which is the subject of this review is identical to Corey's original approach and therefore will not be discussed at this time.

The goal of the present study is part of a larger ongoing effort in our research laboratories geared towards not only developing efficient methodology for the construction of forskolin, but also general methodology that

can be applied to the construction decalin systems present in many natural products.

Scheme 2-11



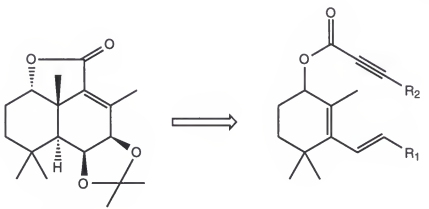
General Objectives

As stated earlier, the present study focuses on the efficient elaboration of the A-B ring system. As in many pervious reports, an intramolecular Diels-Alder approach is used, as illustrated in Scheme 2-12.

Commercially available α-ionone **(3)** is used as the starting material and converted into a variety of diene and triene systems used in both intra- and intermolecular

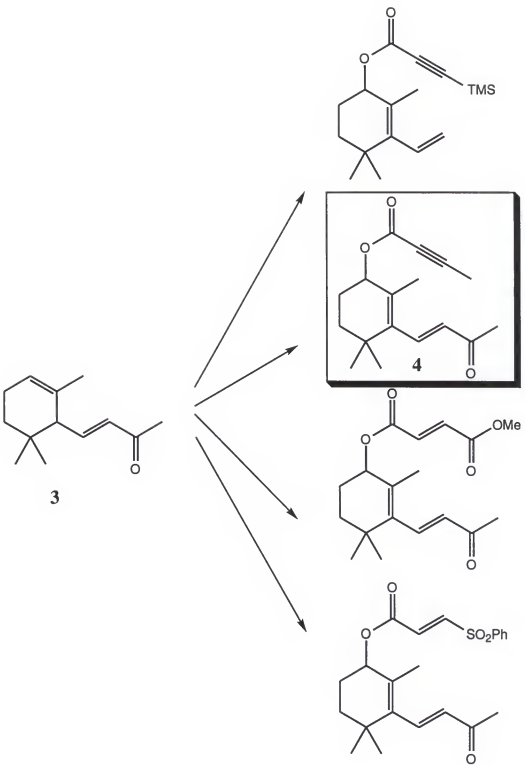
studies. Scheme 2-13 contains a few of the systems that were constructed. The study also reports on the electronic and steric effects of various substituents on the triene system. It was found that under thermal conditions, very small changes in the conditions of the reaction can lead to different products. A study regarding the cyclization of triene **4** was carried out and the respective products were characterized by X-ray crystallography.[35]

Scheme 2-12



215

Scheme 2-13



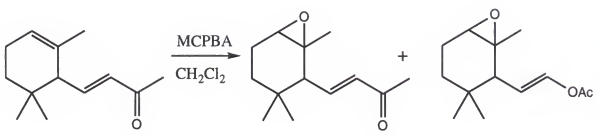
Synthesis of Triene Systems

Our initial approach to the construction of intramolecular adducts was similar to the one published by Corey, but developed independently in our laboratories.[36] The ionone starting material was initially epoxidized selectively on the more electron rich olefin to yield epoxyionone **6** along with a minor product resulting from the Bayer-Villiger oxidation of the unsaturated methyl ketone to the acetyl enol ether **6a** (Scheme 2-14). This product was minimized to less than 5% after optimization of the reaction conditions (e.g. cooling with an ice bath and controlled addition of the oxidizing agent over 8 hours). While not our desired product, **6a** still represented an interesting candidate for cycloaddition, being a more activated diene system than **6**. Attempts were made in preparing **6a** as the only product using 2 equivalents of oxidizing agent. However, the reaction did not proceed cleanly and still yielded a considerable amount of **6** (55%), as shown by gas chromatography. Since **6a** was not our intended target, no further effort was invested in studying this reaction.

The reaction was therefore carried out as shown in Scheme 2-15 using one equivalent of MCPBA and afforded **6** as the only product observed by NMR, and identified by the presence of two signals for the now diastereotopic gem dimethyl functionality and the absence of one of the vinyl protons from the ionone starting material. Carbon NMR further

confirmed the product by the disappearance of two vinyl signals.

Scheme 2-14

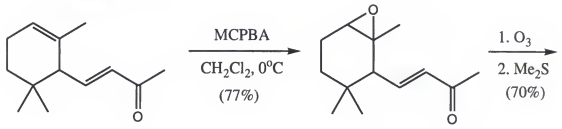


3 **6** **6a**

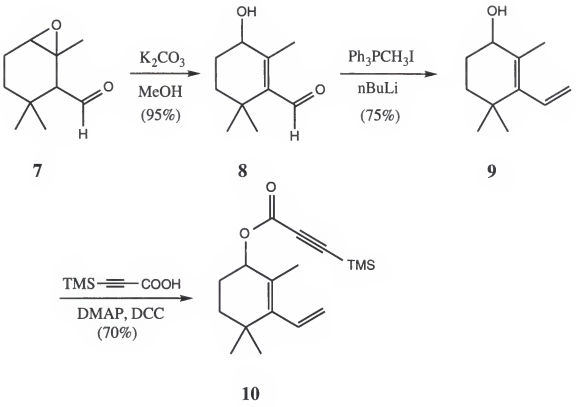
The synthesis continued with the conversion of **6** into citral **7** by ozonolysis. Corey's synthesis involves an additional step by first reducing the ketone functionality to the allylic alcohol. We have found that by carefully controlling reaction times, this step can be avoided. Direct ozonolysis of **6** afforded **7** in good yield, characterized by the disappearance of the trans vinyl proton signals and the appearance of an aldehyde signal at 9.58 ppm as a small doublet. Purification was found to be somewhat tedious due to the relatively small difference in polarity between **7** and **6**, but on large scale procedures it was found that it is unnecessary, since the ozonolysis proceeded cleanly. Base catalyzed opening of **7**, afforded a system with two vinyl carbons and an alcohol proton in the NMR spectra, identified as **8**. Reaction with methyl triphenyl phosphonium iodide in the presence of nBuLi afforded hydroxydiene **9** in good yield,

characterized by the presence of three new vinyl signals and the absence of the aldehyde signal in both proton and carbon NMR. Esterification of **9** with TMS propynoic acid afforded **10**. The proton NMR spectrum of **10** was somewhat complicated by the fortuitous superimposition of the α-oxygen proton in the ester with one of the vinyl signals. However, this observation, coupled with the disappearance of the corresponding signal present in the starting material at 4.0 ppm further confirmed the formation of adduct **10**. As part of the goal of our study we were interested in investigating the role of the thermodynamic stability of the diene system in the cycloaddition. We recognized that the presence of an electron withdrawing group at the terminus of the diene would have a negative effect on the activity of the diene in the intramolecular cycloaddition, but hoped that the increase in stability would reduce side reactions which result in decomposition or polymerization observed otherwise in vinyl cyclohexenes.

Scheme 2-15



3 **6**

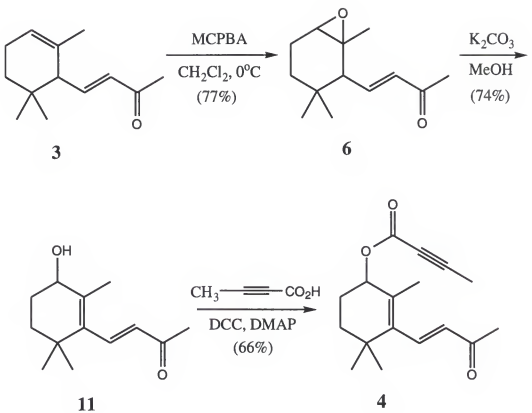


7 **8** **9**

10

We therefore modified our synthesis to construct stabilized triene systems as shown in Scheme 2-16. The same ionone starting material was used and converted to the same epoxide **6**. Base catalyzed opening of this epoxide afforded allylic alcohol **11** in excellent yield, characterized by the presence of two new vinyl carbon signals and the appearance of a clean trans-alkene proton system with a 14 Hz coupling constant. While the magnitude of the coupling constant did not fully confirm the stereochemistry about the olefin, the similarity between this coupling constant and the one present in the ionone starting material of known stereochemistry led us to believe that the stereochemistry was maintained.

Scheme 2-16



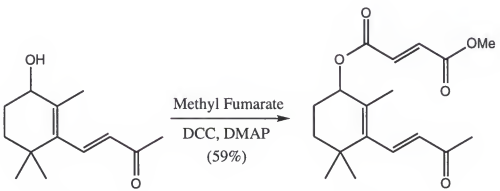
With the hydroxydiene in hand, we proceeded to the esterification with butynoic acid, in hope to have a system that would directly introduce the methyl functionality at C-8. The formation of ester **4** was confirmed by the shifting of the same α-oxygen proton downfield to 5.3 ppm in the product from 4.05 ppm in the free alcohol.

One obvious drawback of this triene is the absence of a second activator on the dienophile component. Corey and co-workers clearly established that a doubly activated

dienophile is desirable in this otherwise sterically hindered intramolecular cycloaddition.

In order to achieve this goal, we embarked on the synthesis of a dienophile that is doubly activated, making it a good candidate for acid catalysis. The same diene component was used, but it was coupled with monomethyl fumarate for increased activation, as illustrated in Scheme 2-17.

Scheme 2-17



7 12

However, even if the fumarate ester will undergo facile cycloaddition, the problem of replacing an ester substituent with a methyl group would add several steps to our route. Therefore, the ideal dienophile should be doubly activated, and also allow easy replacement of the activator with a methyl group after the cycloaddition. 3-phenyl sulfonyl propenoic acid was considered to be a candidate that meets our requirements. The synthesis, shown in Scheme 2-18, started with the reaction between ethyl acrylate and benzene

sulfenyl chloride to afford chlorosulfenyl ester **13**, which was directly converted to the sulfone analog **14** using MCPBA. Base-catalyzed elimination using DBU afforded the trans unsaturated system as the major product, as confirmed by the 15 Hz coupling constant between the two vinyl protons. The most challenging step in this synthesis proved to be the hydrolysis of the ester to the carboxylic acid. Several attempts were made using basic conditions such as LiOH/MeOH, NaOH/MeOH, and even mild acidic conditions at room temperature. It was found that 4M HCl under reflux hydrolyses the ester over very long reaction times (50% conversion after 60 hours). The acid was then coupled with the same diene system as the monomethyl fumarate to afford the equivalent ester **17**.

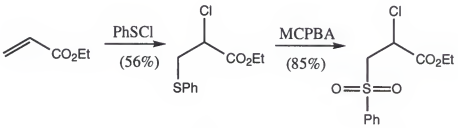
Intramolecular Diels-Alder Studies

Our initial work using the vinyl-cyclohexene-type adducts confirmed previous observations in our group referring to the instability of these systems. For example, attempts to carry out the cyclization of adduct **10** resulted in only trace amounts of cycloadduct and mainly in decomposition products. We attribute this observation to the ease of polymerization that characterizes vinyl cyclohexenes.

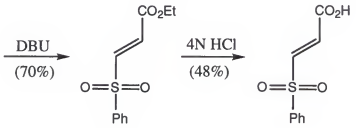
In order to increase the stability of such systems, adducts such as butynoate **4** were prepared. Attempts to carry out cycloaddition revealed the relatively high thermal stability of these systems. Even at temperatures of 150°C,

while no cycloaddition was observed, **4** was isolated with no major decomposition observed. In order to reach higher temperatures, a sealed tube was employed. While this allowed us to reach temperatures of 180°C, it prevented us from monitoring the reaction. After 18 hours, a cycloadduct was formed. We expected the structure to be consistent with **18**, shown in Scheme 2-19.

Scheme 2-18

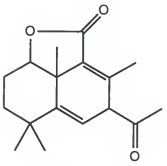


13 **14**



15 **16**

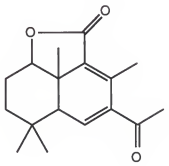
Scheme 2-19



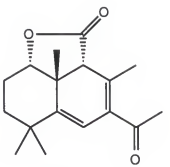
18

However, upon careful examination of the ^{1}H NMR spectrum we observed an inconsistency with **18**, in that the proton signal at C5 was a singlet, while it was expected to be a doublet. Mass spectroscopy confirmed that no mass was lost and UV spectroscopy confirmed the presence of a conjugated system, which allowed us to discount the possibility of an undesired side reaction. At such high temperatures, a migration of a double bond seemed a reasonable assumption. Scheme 2-20 shows the other two isomers that could be obtained. While **19** has the advantage of being a highly conjugated system, it has two shortcomings in that it still has a "bridgehead" double bond, therefore not relieving any strain present in **18**, and it still has a proton at C5 that should be a doublet. On the other hand, **20** addresses both problems, in that while still being a conjugated system, it has the C5 proton as a singlet and is presumed to be favored thermodynamically due to the absence of a "bridgehead" double bond. In order to confirm the rather complex 2D NMR of the adduct, we prepared a single crystal for crystallographic analysis. This allowed us to not only confirm our NMR assignments for the migration of the double bond, but also gave us a higher degree of confidence in the stereochemical assignment of the C8a methyl substituent.

Scheme 2-20

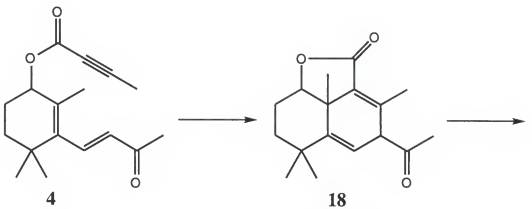


19



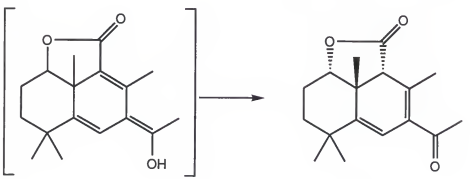
20

Scheme 2-21



4

18



20

Careful analysis of the crystallographic data indeed confirmed our assumption that the lack of coupling at the C5 proton was not due to an orthogonal relationship with the adjacent proton, but due to the isomerization of one of the double bonds. Mechanistically this can be rationalized by the formation of the highly conjugated enol of the methyl ketone substituent at C4 and reformation of the ketone in its isomeric form, as shown in Scheme 2-21.

Figure 1 contains the molecular structure of the adduct with 50% probability ellipsoids showing the atom numbering scheme. The positional parameters and equivalent isotropic thermal parameters of the non-H atoms are listed in Table 1, and a selected set of bond lengths and angles are listed in Table 2. Tables of anisotropic thermal parameters , H-atom positional parameters and bond length and angels, as well as the structure-factor amplitudes are present in the Appendix.

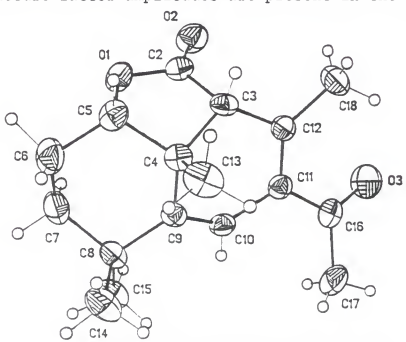


Figure 1: X-ray Structure of **20**

Table 1: Fractional coordinates and equivalent isotropic[a] thermal parameters ($Å^2$) for the non-H atoms of compound **20**.

Atom	x	y	z	U
O1	0.6586(3)	0.2952(2)	0.3367(2)	0.0497(8)
O2	0.6043(3)	0.1472(2)	0.4290(2)	0.0583(9)
O3	0.4789(4)	0.3309(3)	0.7122(2)	0.0712(11)
C2	0.6585(4)	0.2470(3)	0.4147(2)	0.0420(10)
C2a	0.7332(4)	0.3381(3)	0.4746(2)	0.0361(10)
C3	0.6665(4)	0.3319(3)	0.5611(2)	0.0359(9)
C4	0.5500(4)	0.4108(3)	0.5787(2)	0.0355(9)
C5	0.4930(4)	0.4950(3)	0.5132(2)	0.0374(10)
C6	0.4989(4)	0.6041(3)	0.3736(2)	0.0452(11)
C7	0.5128(5)	0.5364(4)	0.2894(2)	0.0541(13)
C8	0.6739(5)	0.4943(4)	0.2690(3)	0.0585(14)
C8a	0.7420(4)	0.4137(3)	0.3364(2)	0.0460(11)
C8b	0.7247(4)	0.4617(3)	0.4272(2)	0.0374(9)
C8c	0.5669(4)	0.5204(3)	0.4418(2)	0.0365(9)
C9	0.8592(5)	0.5467(4)	0.4524(3)	0.0555(14)
C10	0.7327(6)	0.2355(5)	0.6177(3)	0.057(2)
C11	0.4745(4)	0.4167(3)	0.6630(2)	0.0437(10)
C12	0.3961(7)	0.5347(5)	0.6877(3)	0.067(2)
C13	0.3280(5)	0.6333(4)	0.3892(3)	0.0573(15)
C14	0.5833(7)	0.7295(4)	0.3693(4)	0.066(2)

[a]For anisotropic atoms, the U value is U_{eq}, calculated as $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* A_{ij}$ where A_{ij} is the dot product of the i^{th} and j^{th} direct space unit cell vectors.

Table 2: Bond Lengths (Å) and Angles (°) for the non-H atoms of compound **20**.

1	2	3	1-2	1-2-3
C2	O1	C8a	1.347(4)	109.9(3)
C8a	O1		1.468(4)	
C2	O2		1.196(4)	
C11	O3		1.214(4)	
C2a	C2	O1	1.516(5)	109.3(3)
C2a	C2	O2		129.1(3)
O1	C2	O2		121.6(3)
C3	C2a	C8b	1.495(4)	118.3(3)
C3	C2a	C2		112.8(3)
C8b	C2a	C2	1.535(4)	103.5(3)
C4	C3	C10	1.348(4)	127.0(3)
C4	C3	C2a		116.9(3)
C10	C3	C2a	1.492(6)	116.1(3)
C5	C4	C11	1.469(4)	117.7(3)
C5	C4	C3		119.6(3)
C11	C4	C3	1.495(5)	122.7(3)
C8c	C5	C4	1.334(5)	124.9(3)
C7	C6	C8c	1.533(5)	108.1(3)
C7	C6	C13		108.4(3)
C8c	C6	C13	1.530(5)	112.2(3)
C8c	C6	C14		111.6(3)
C13	C6	C14	1.532(6)	106.5(3)
C14	C6	C7	1.540(6)	110.0(3)
C8	C7	C6	1.501(6)	114.0(3)
C8a	C8	C7	1.503(6)	112.6(3)
C8b	C8a	O1	1.545(5)	104.0(3)
C8b	C8a	C8		115.9(3)
O1	C8a	C8		108.3(3)
C8c	C8b	C9	1.522(4)	113.0(3)
C8c	C8b	C2a		109.2(3)
C8c	C8b	C8a		111.7(3)
C9	C8b	C2a	1.535(5)	110.8(3)
C9	C8b	C8a		111.9(3)
C2a	C8b	C8a		99.5(2)
C5	C8c	C6		122.9(3)
C5	C8c	C8b		118.3(3)
C6	C8c	C8b		118.8(3)
C12	C11	O3	1.496(6)	119.6(3)
C12	C11	C4		118.1(3)
O3	C11	C4		122.3(3)

Some noteworthy features of structure **20** are that ring A adopts the most stable chair, $_1C^4$, conformation, and atoms C7

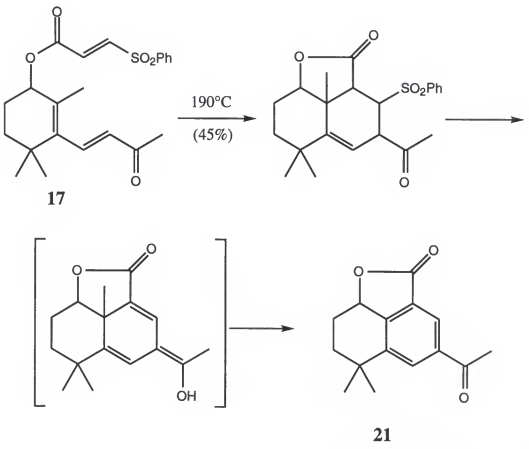
and C8b lie at distances of -0.63(1) Å and 0.50(1) Å from the least squares plane of atoms C8, C8a, C8c and C6. The furan ring adopts an envelop, E^5, conformation. Atom C8b occupies the flap position and lies at the distance of 0.58(1) Å from the least squares plane of the rest of the atoms in the ring. That the two double bonds in ring B are twisted with respect to each other was evidenced by a torsion angle -15.2(2)° of C3-C4-C5-C8c. The acetyl group is also twisted out of the plane of ring B; torsion angle of C3-C4-C11-O3 is -22.1(2)°.

With adduct **20** in hand, we attempted the oxygenation of the olefin functionalities. Treatment with one equivalent MCPBA afforded the epoxide of the C3-C4 olefin, while the C5-C8c epoxide was desired. The characterization of this product was done by Dr. Ivani Malvestiti[36] using X-ray crystallography. In order to avoid this problem, we attempted the cyclization of **17**, which has several clear advantages over **4**. First, the dienophile component is more activated and is therefore expected to react at lower temperatures. Secondly, the new six-membered ring generated is now a cyclohexene and not a cyclohexadiene, which eliminates the selectivity problem during the epoxidation step. Thirdly, the C2a-C3 olefin can easily be installed by the elimination of phenylsulfonic acid, an adequate leaving group.

To our disappointment, attempts to carry out the cyclization at lower temperatures failed, probably in part due to the *trans* geometry of the dienophile. At temperatures of 190°C, a new cyclization product, **21**, was observed. The

characterization of **21** using NMR was relatively straight forward. However, due to the presence of a "blocking group" at C8b stronger evidence was required to unequivocally prove this unexpected product, shown in Scheme 2-22. The sample was recrystallized and submitted by Dr. Ivani Malvestiti for X-ray analysis, confirming the assigned structure.[36a]

Scheme 2-22

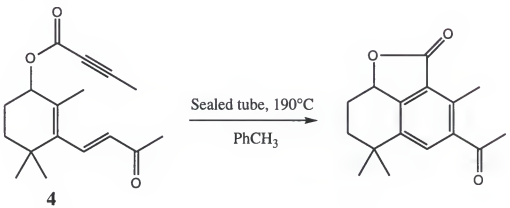


17 **21**

In an attempt to reconcile the results obtained in the cycloaddition of **4** with the cycloaddition of **17**, which presumably must initially form almost the same intermediate

(less the C3 methyl substituent), we repeated the former under the same conditions as the latter. As expected the aromatized product, equivalent to **21**, was isolated, as illustrated in Scheme 2-23.

Scheme 2-23



4

Conclusion

The present study once again demonstrates the applicability if the intramolecular Diels-Alder cycloaddition to the efficient construction of tricyclic natural products. While unarguably a very powerful method, this reaction clearly has limitations, as demonstrated by our results. Despite the favorable entropy factor that differentiates intramolecular from intermolecular processes, the same precautions taken with intermolecular system must be considered. While steric constraints can be overcome by

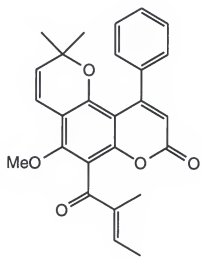
higher temperatures, we have demonstrated the effects of temperature on the structure of the adduct.

CHAPTER 3
SYNTHESIS OF A 3,4-DIHYDRO-*2H*-PYRAN-6-YL-METHANAL INTERMEDIATE FOR THE CONSTRUCTION OF A NEW CLASS OF HETERODIENES

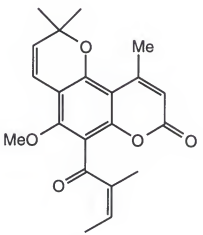
Introduction

Dipyranocoumarins are a group of natural products isolated from several tropical plants of the genus *Calophyllum*,[36] and are characterized by coumarin, chromene and chromane ring systems, usually assembled around a phloroglucinol core.[37] Over the past 35 years, more than 20 different pyranocoumarins were isolated.

Scheme 3-1



Calophyllolide



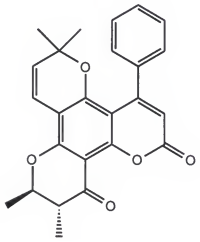
Oblongulide

Pyranocoumarins can be structurally subdivided into three series[38] based upon the nature of a common 2-methylbut-2-enoyl group, or its modification, attached to the aromatic ring.

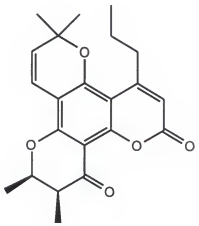
Series A is characterized by the presence of the 2-methylbut-2-enoyl group in the uncyclised form and includes some of the structures depicted in Scheme 3-1.

Series B pyranocoumarins possess a 2,3-dimethyl chromanone ring resulting from the cyclization of the 2-methylbut-2-enoyl group with the *ortho* oxygen, as shown in Scheme 3-2.

Scheme 3-2



Inophyllum C



Calanolide D

Series C, the largest group, contains a 2,3-dimethylchromanol ring resulted from the cyclization and reduction of the 2-methylbut-2-enoyl moiety and will be the

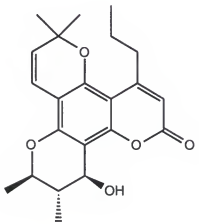
focus of our study. Some of the more important representatives, shown in Scheme 3-3, are the Calanolides, **22** and **23**, isolated from *Callophyllum Lanigerum*.[39] Recent interest in these natural products has increased as a result of their identification as potent representative of a pharmacologically distinct subclass of non-nucleosidal inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).[36] While many of the pyranocoumarins exhibit this activity, the calanolides were one of the few that were reported to be highly active in inhibiting HIV-1 replication and were active even against the AZT-resistant HIV-1 strain G-9106 and the pyridinone-resistant HIV-1 strain A17. Since the extraction and isolation from natural sources provides only 0.1% of **22**, a more adequate supply is needed to conduct conclusive clinical tests. Benzopyran structures are also present in aldose reductase inhibitors,[40] potassium channel openers,[41] and antiarrythmic drugs,[42] making them important synthetic targets.

The present study reports a general approach to the construction of pyranocoumarins, as structure-activity relationship studies will require a wide variety of unnatural as well as naturally occuring systems.

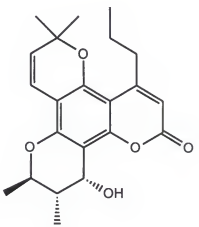
Since the first reports on the biological activity of the Calanolides, many research groups in academia as well as the pharmaceutical industry have embarked on the total synthesis of **22** and **23**.[43] The published syntheses to date all use phloroglucinol as a starting material and are based on

typical aromatic transformations that generally require extremely harsh conditions (strong Lewis or Bronstedt acids, etc.). Due to the similarity of the approaches only the most recent synthesis published by Keppler[44] in 1996 will be discussed.

Scheme 3-3



Calanolide A **22**



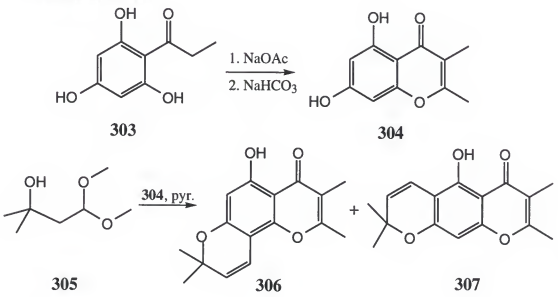
Calanolide B **23**

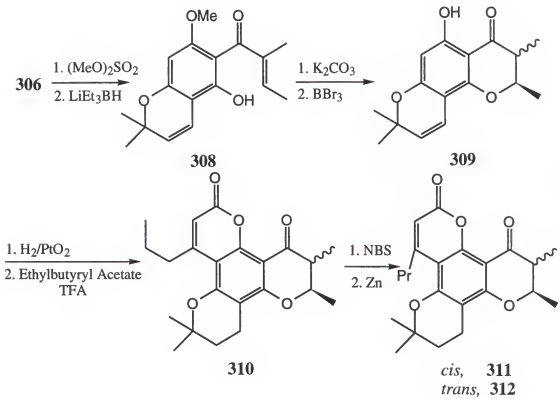
Keppler's approach is summarized in Scheme 3-4. While quite convergent, the route has some major shortcomings, in that several transformations afford a mixture of regioisomers therefore reducing the commercial applicability of the method. Starting with a derivative of phloroglucinol, **303**, through a Kostanecki-Robinson reaction, Keppler prepares intermediate **304** which is then reacted with alcohol **305** to yield a 3:1 mixture of **306** and **307**. The reaction of **306** with dimethylsulfate, followed by reduction with lithiumtriethylborohydride led to the formation **308**.

Treatment of **308** with potassium carbonate , followed by demethylation of the phenyl ether with boron tribromide gave the desired intermediate **309** again as a 1:1 mixture of *cis* and *trans* isomers. Reduction of **309**, followed by treatment with ethylbutyrylacetate in refluxing trifluoroacetic acid gave **310** as an inseparable *cis/trans* mixture. Bromination with N-bromosuccinimide followed by dehydrohalogenation afforded a separable mixture of **311** and **312,** the latter being converted to Calanolide A.

From this method as well as from the others published, it is clear that an alternate method that addresses the construction of the chiral moiety needs to be developed. The current methods not only do not afford chiral materials, but also generate 50% of the wrong diastereomer in the later part of the synthesis, which is unacceptable for practical applications.

Scheme 3-4





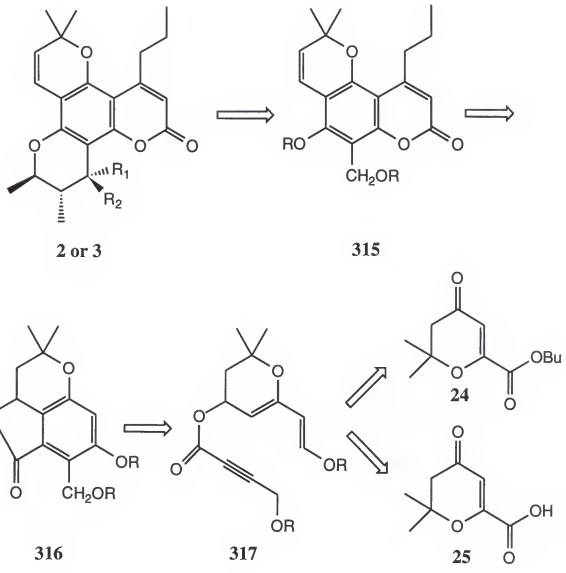
Our method attempts to address this problem by using a fundamentally different approach based on an intramolecular Diels-Alder reaction, which allows for greater flexibility in the elaboration of the ring containing the chiral centers.

Retrosynthetic Analysis

Due to the emphasis in the flexibility of the method, several retrosynthetic approaches will be studied. Scheme 3-5 contains a representative example of our approach. The first disconnection removes the ring containing the chiral centers and reveals **315**. A Bayer-Villiger disconnection reveals the 5-membered lactone in **316**, while ring C can be installed

using a Friedel-Crafts alkylation. The key disconnection, which involves the intramolecular cycloaddition exposes **317** as the required triene system. We envision the preparation of this material from commercially available materials such as **24** or **25**.

Scheme 3-5

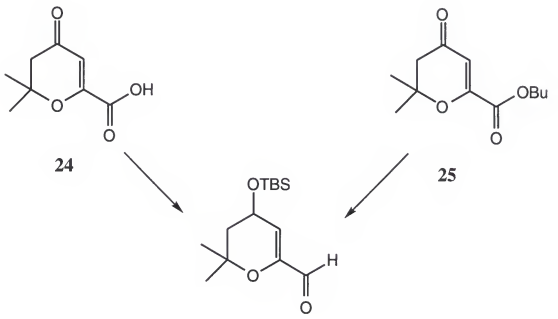


2 or 3 **315** **316** **317** **24** **25**

Results and Discussion

In an attempt to construct a large variety of diene systems, we first set out to developed a method for the convenient preparation of aldehyde **31**, the common intermediate to all our diene systems, shown in Scheme 3-6.

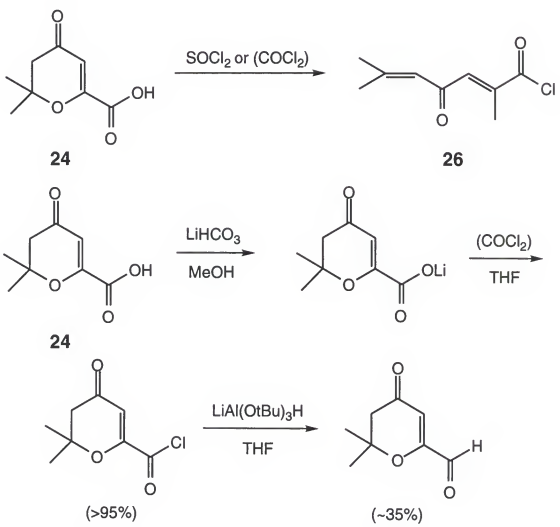
Scheme 3-6



Two approaches were examined for this route using the commercially available ketoacid **24** and ketoester **25**. Reaction of the ketoacid **24** (Scheme 3-7) with either thionyl or oxallyl chloride gave the open form of the pyran ring **26**, via most likely an acid-catalyzed opening. In order to avoid the presence of acid, the reaction was run under basic conditions

in the presence of triethyl amine, but unsatisfactory results were obtained in this case as well.

Scheme 3-7



24 **26** **24** **27**

Therefore, we turned our attention to neutral conditions, first converting the carboxylic acid into the carboxylate salt, followed by the reaction with oxallyl chloride to yield **27** in almost quantitative yield. However,

reduction of the acid chloride did not prove to be an efficient route to the ketoaldehyde, due to the difficulty of recovering the product from the aluminum salts formed. The use of the ketoacid was therefore abandoned in favor of the less expensive butyl ester, also known as Butopyronoxyl. However, due to its α,β-unsaturated γ-ketoester functionality, atypical behavior towards common reducing agents was anticipated. Two modes of reduction are available to such systems, 1,2- and 1,4-addition of the hydride leading to an allylic alcohol or saturated ketone (or alcohol), respectively. Previous studies have concluded that the relative importance of the two paths may be rationalized using hardness-softness arguments, 1,2-addition being a charge-controlled process, while 1,4-addition is a frontier orbital controlled process.[45] According to this concept, hard metal hydrides are expected to add preferentially to the 2-position, whereas soft metal hydrides add to the 4-position of the conjugated system.[46]

The reducing agents used in our studies were diisobutylaluminum hydride (DIBAL-H) and lithium aluminum hydride. The former is expected to selectively afford 1,2 reduction products,[47] while the latter may give 1,2- or 1,4-reduction products, depending on conditions.[48] Factors such as polar solvents or addition of cryptands have been shown to favor 1,4-reductions.[49, 50] The 1,4 reductions are believed to proceed via either a polar or a radical mechanism with initial complexation of the aluminum reagent at the carbonyl

carbon, where the hydride is then within bonding distance of the β carbon, regardless of the anionic or radical nature of the process.[50]

In fact, despite previous reports[47] that DIBAL-H affords exclusively 1,2 reduction products, for α,β-unsaturated esters, we have uncovered an example whereby, 1,4-reduction is a reality under the proper conditions (Table 3, entry 3).[51] The table illustrates the fact that in the case of a polar solvent, such as THF, precoordination of the aluminum reagent to the ester carbonyl oxygen of **24** renders one equivalent of DIBAL-H unavailable for reduction (entry 1); however, a second equivalent of DIBAL-H cleanly affords the expected allylic alcohol in high yield as the only product (entry 2), whereas a third equivalent of DIBAL-H reduces the unsaturation in the molecule (entry 3). This effect can largely be attributed to the precoordination of the aluminum reagent to the ester carbonyl oxygen, making the α,β-unsaturated ester a better Michael acceptor (Scheme 3-8). As expected, complete saturation was observed in the case of lithium aluminum hydride (entry 4).

In order to probe this coordination effect on the internal delivery of the hydride, as presented in Scheme 3-8, the DIBAL-H reduction of **24** was carried out in hexanes (Table 3, entry 5), a solvent that does not favor precoordination. Under these conditions the allylic alcohol **28** was isolated as the sole product in good yield requiring only one equivalent of reducing agent. Furthermore, with excess DIBAL-H (4.5 eq)

in hexanes both carbonyl functions were reduced while maintaining the ring unsaturation (Table 3, entry 6). As a further precaution against 1,4-reduction, and to facilitate the final oxidation step, the hydroxyl group in **28** was protected before the reduction of the ester group, as shown in Scheme 3-9.

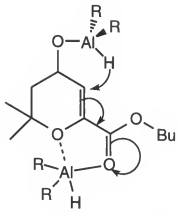
Table 3. Reactions of **24** with DIBAL-H and $LiAlH_4$.

Entry	Reagent	Equiv.	Conditions	Products/Yield
1	DIBAL-H	1.1	THF, 0°C	+ S.M. (48%)
2	DIBAL-H	2.2	THF, 0°C	(90%)
3	DIBAL-H	3.2	THF, 0°C	+ (25%) (45%)
4	$LiAlH_4$	2.1	THF, -35°C	+ (45%) (24%)
5	DIBAL-H	1.1	Hexanes, 0°C	(90%)
6	DIBAL-H	4.5	Hexanes, 0°C	+ OTHER PRODUCTS[12] (48%)

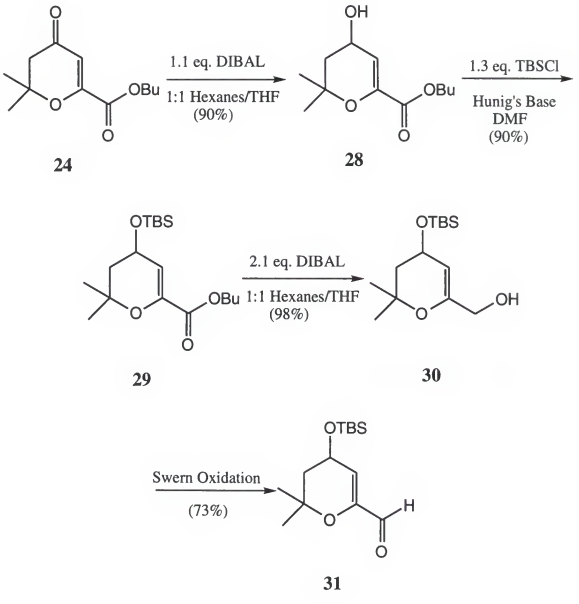
Treatment of **24** with one equivalent of DIBAL-H in a 1:1 Hexanes:THF solvent mixture cleanly generated alcohol **28**.

Protection of the alcohol as the t-butyldimethylsilyl ether, followed by a second DIBAL-H reduction affords alcohol **30**, which is subsequently oxidized[52] to the target aldehyde **31** in 58 % overall yield. Alternatively, alcohol **28** could be directly reduced to aldehyde **31**, but the process has been found to have significant scaleup problems. The workup procedure described[53] for DIBAL-H reductions using Rochelle's Salt was found to be extremely convenient and practical, especially on large scale reactions.

Scheme 3-8



Scheme 3-9

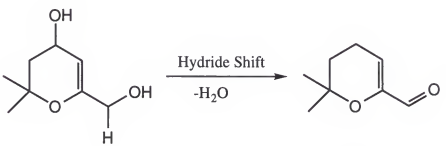


24 **28** **29** **30** **31**

In an attempt to shorten the synthesis of **31** and broaden the scope of our reductive studies, the reduction of **24** using 3 equivalents of DIBAL in hexanes was carried out. The expected doubly allylic diol, **32**, was indeed obtained. Surprisingly, this product was found to be extremely unstable and therefore difficult to isolate and purify. During an

attempted distillation of **32** under reduced pressure we isolated a new aldehyde as the only product, as shown in Scheme 3-10. Presumably this product is formed via a hydride shift mechanism. While this product was at the time unexpected and unusual, further studies discussed in a later chapter confirmed that other pyran-allylic alcohols undergo similar processes. Attempts to carry out this process in the presence of various acids were hindered by the relatively high instability of **32** to acidic conditions. However, the formation of **33** was observed in the presence of triethylamine hydrochloride in moderate yields.

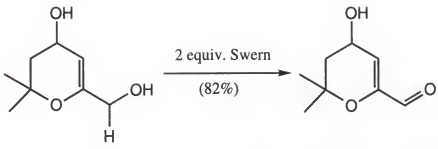
Scheme 3-10



32 **33**

Since purification of **32** proved to be impractical on large scale reactions, we attempted the Swern[52] oxidation using crude diol and observed that the Swern conditions are not sufficient to oxidize the secondary alcohol and yield aldehyde **34** even in the presence of two equivalents of oxidizing agent, as shown in Scheme 3-11.

Scheme 3-11

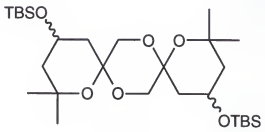


32 **34**

During an attempted Swern oxidation of **30** using a modified procedure requiring excess oxallyl chloride (2.2 equiv. oxallyl chloride, 2.2 equiv. dimethyl sulfoxide and 5 equiv. triethyl amine, versus 1.1 equiv. oxallyl chloride, 2.2 equiv. dimethylsulfoxide and 5 equiv. triethyl amine more commonly used), we observed the formation of a new diastereomeric mixture of two products as a white solid. Attempts to characterize this product mixture using NMR spectroscopy were unsuccessful due to the simplicity of the NMR pattern. In order to gain some insight in the mechanistic nature of the process, we assumed that the increase in acidity of the conditions in the Swern oxidation caused the formation of this product and attempted to obtain the same product under controlled acidic conditions. Several Bronstedt and Lewis acids were tested and the best results in replicating the findings from the Swern study were obtained using triethylamine hydrochloride in ether. The most significant piece of information about this mixture was

revealed by the high resolution chemical ionization mass spectrum, which showed a mass peak consistent with the formation of a dimeric structure. The absence of vinyl signals in the proton NMR, correlated with the fact that the mechanism was of an acidic nature, indicating that a protonation of the alkene is likely to be part of the process. We therefore proposed structure **35**, shown in Scheme 3-12 as a possible product.

Scheme 3-12



35

In order to establish the relative stereochemistry of the two products, a fractional recrystallization technique was used, affording single crystals used for X-ray analysis of one diastereomer. The X-ray results confirmed the formation of structure **35** and Figure 2 contains the molecular structure of the adduct with 50% probability ellipsoids showing the atom numbering scheme. As expected, all three cyclohexane rings adopt a chair conformation. Noteworthy is the axial placement of O1 and O1a relative to the center ring, as well as the equatorial placement of the tert-butyl

dimethyl silyl ether substituents. The positional parameters and equivalent isotropic thermal parameters of the non-H atoms are listed in Table 4, and a selected set of bond lengths and angles are listed in Table 5. Tables of anisotropic thermal parameters , H-atom positional parameters and bond length and angles, as well as the structure-factor amplitudes are present in the Appendix.

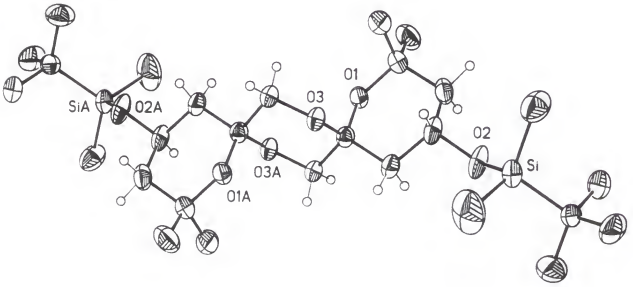


Figure 2: X-ray structure of Dimer **35**.

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **35**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

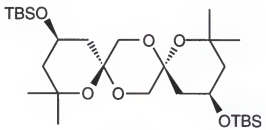
Atom	x	y	z	U(eq)
Si	6674(1)	978(1)	8198(1)	36(1)
O1	9073(1)	-1296(1)	5525(1)	32(1)
C2	8920(2)	-1781(2)	6679(2)	39(1)
C3	7901(2)	-1309(2)	6945(2)	42(1)
C4	7925(2)	-141(2)	6996(2)	38(1)
C5	8075(2)	287(2)	5745(2)	35(1)
C6	9053(2)	-203(1)	5423(2)	28(1)
C7	8981(2)	42(2)	4018(2)	30(1)
O8	9960(1)	-257(1)	3714(1)	30(1)
C9	8705(3)	-2913(2)	6260(3)	56(1)
C10	9965(2)	-1687(2)	7867(2)	52(1)
O11	6875(1)	224(1)	7068(2)	48(1)
C12	7290(2)	388(3)	9841(3)	60(1)
C13	7329(4)	2264(3)	8180(5)	90(1)
C14	5116(2)	1074(2)	7745(2)	36(1)
C15	4614(3)	1594(3)	6412(3)	62(1)
C16	4619(2)	-14(2)	7675(3)	51(1)
C17	4802(3)	1710(2)	8777(3)	59(1)

Table 5. Bond lengths [A] and angles [deg] for **35**.

Si-O11	1.640(2)
Si-C12	1.856(3)
Si-C13	1.857(3)
Si-C14	1.879(2)
O1-C6	1.414(2)
O1-C2	1.457(2)
C2-C9	1.526(3)
C2-C10	1.527(3)
C2-C3	1.534(3)
C3-C4	1.508(3)
C4-O11	1.435(2)
C4-C5	1.523(3)
C5-C6	1.524(3)
C6-O8#1	1.429(2)
C6-C7	1.521(3)
C7-O8	1.431(2)
O8-C6#1	1.429(2)
C14-C15	1.529(3)
C14-C16	1.530(3)
C14-C17	1.532(3)
O11-Si-C12	110.34(12)
O11-Si-C13	110.3(2)
C12-Si-C13	108.8(2)
O11-Si-C14	104.04(8)
C12-Si-C14	111.41(11)
C13-Si-C14	111.9(2)
C6-O1-C2	119.35(14)
O1-C2-C9	102.6(2)
O1-C2-C10	111.6(2)
C9-C2-C10	110.5(2)
O1-C2-C3	109.6(2)
C9-C2-C3	110.7(2)
C10-C2-C3	111.6(2)
C4-C3-C2	113.2(2)
O11-C4-C3	108.7(2)
O11-C4-C5	107.8(2)
C3-C4-C5	109.7(2)
O1-C6-O8#1	111.9(2)
O1-C6-C7	106.2(2)
O8#1-C6-C7	109.1(2)
O1-C6-C5	113.1(2)
O8#1-C6-C5	106.6(2)
C7-C6-C5	110.1(2)
O8-C7-C6	112.9(2)
C6#1-O8-C7	112.44(14)
C4-O11-Si	126.76(13)
C15-C14-C16	108.3(2)
C15-C14-C17	108.7(2)
C16-C14-C17	109.3(2)
C15-C14-Si	111.3(2)
C16-C14-Si	109.5(2)
C17-C14-Si	109.8(2)

The structure of the molecule explains the relative simplicity of the NMR pattern due to the presence of a C_2 axis of symmetry. The fact that the other diastereomer exhibits a very similar pattern indicates that its basic skeleton should also have a C_2 axis. A possible structure of the second diastereomer is shown in Scheme 3-13.

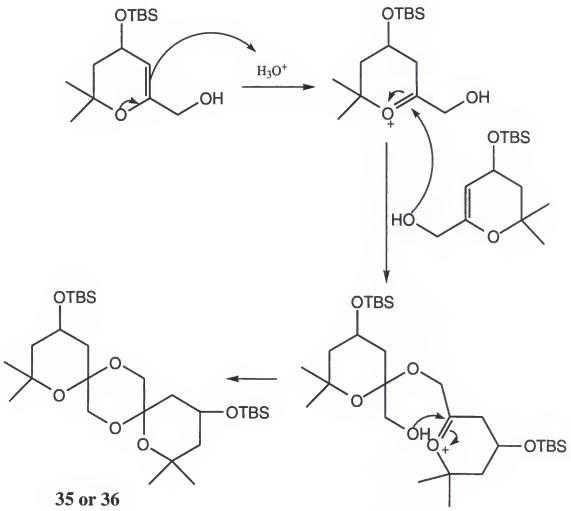
Scheme 3-13



36

From a mechanistic standpoint, the process can be explained by the protonation of the alkene as shown in Scheme 3-14, followed by nucleophilic attack of the oxygen from another molecule of primary alcohol. The process can then be repeated for the other half of the molecule, leading to the observed product.

Scheme 3-14



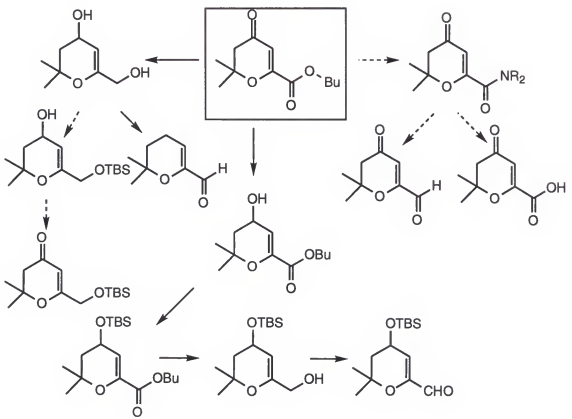
35 or 36

Conclusion

The study presented in this chapter revealed the complexity of relatively simple pyranyl systems in oxidation/reduction processes. We have found that while under normal conditions, the reductions of α,β-unsaturated esters using DIBAL-H occurs in a 1,2 fashion, under certain

conditions, the 1,4-reduction is a reality. Careful control of the conditions therefore adds more flexibility of the method.

Scheme 3-15



Pyranyl systems exhibit far lower thermal and chemical stability than their carbocyclic analogs. For example, under thermal conditions, rearrangements involving hydride shifts can occur, while under even mildly acidic conditions, we observed products ranging from ring-open products to dimeric structures. In the context of our goal to develop routes to pyranocoumarins, the study has allowed the construction of a

wide variety of useful building blocks for the synthesis of natural products (Scheme 3-15).

CHAPTER 4
SYNTHESIS OF A NEW CLASS OF PYRAN-DERIVED HETERODIENES AND TRIENES

Introduction

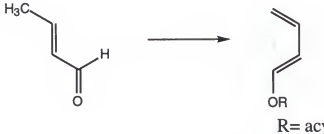
Substitution of dienes with heteroatoms has been employed extensively in the construction of natural products and offers a number of advantages.[55] First and foremost, it activates dienes to react with otherwise unreactive dienophiles such as isolated alkenes and alkynes. Second, it allows easy removal of the activating group after the formation of the product without further functionalization of the product. Last but not least, heteroatom-substituted dienes have been found to enhance the regio- and seteroselectivity of Diels-Alder reactions, especially in Lewis-Acid catalyzed reactions. A wide variety of substituted heterodienes have been employed to date. For the purpose of our study, only oxygen and sulfur substituted dienes will be discussed.

Oxygen-substituted Dienes

Monoalkoxy- and trimethylsilyloxy-1,3-butadienes shown in Scheme 4-1 are some of the first examples of heterodienes used in Diels-Alder reactions. They add to unsymmetrical dienophiles in good yields and with good regio- and

stereoselectivity, leading to *ortho*- or *para*-adducts.[56] The labile groups required can be prepared by the acylation of the enol tautomers of the corresponding carbonyl compounds.

Scheme 4-1



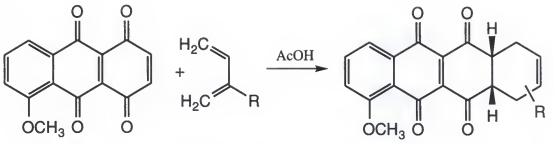
R= acyl, alkyl

R= acyl, alkyl

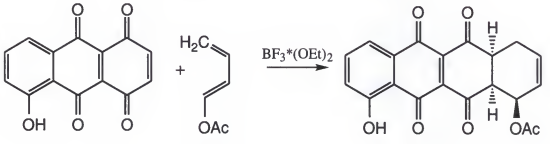
For the synthesis of anthracyclinones, shown in Scheme 4-2, dienes **401** and **404** have proven to be especially useful.[57] In contrast to diene **402** , they are regiospecific in the reaction with diquinone **400**. The regiospecificity can be attributed to the preferential precoordination of the Lewis Acid catalyst to the carbonyl *ortho* to the phenolic oxygen.[58]

A rather elegant alternative to the formation of alkylated analogs of **402** is shown in Scheme 4-3 and based on the thermal rearrangement of prop-2-ynyl acetates.[59]

Scheme 4-2

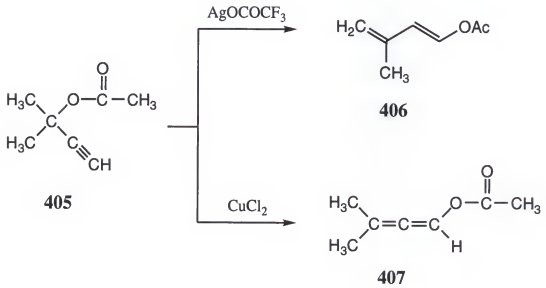


400 **401** R = OAc; **402** R = Et **403**



404

Scheme 4-3

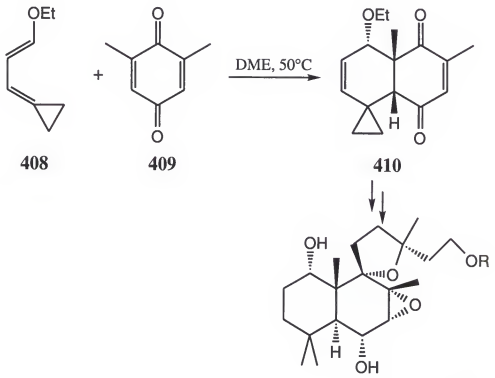


405 **406** **407**

However, the formation of prop-2-ynyl acetates such as **406** is in competition with the allenyl acetate **407**. Careful choice of catalyst systems can reduce or even eliminate the formation of **407**.

A more recent application of the use of heteroatom-substituted dienes is the synthesis of the labdane diterpenoid (±)-erigerol **(411)** (Scheme 4-4).[60] Noteworthy is the fact that diene **408**, aside from the regiodirecting ethoxy group, contains a cyclopropylidene moiety which serves as an equivalent for the significantly less reactive 1-ethoxy-4-methyl-1,3-pentadiene.

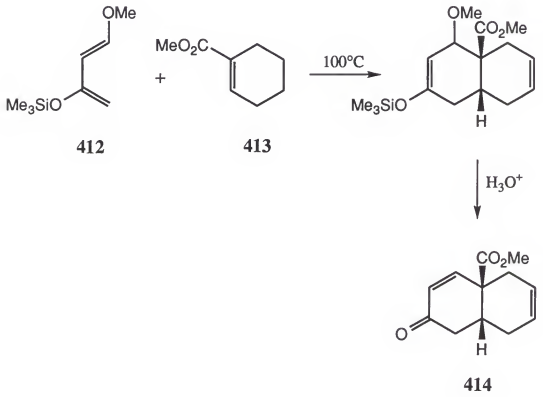
Scheme 4-4



408 **409** **410** **411**

One of the most popular dioxygenated dienes is 1-methoxy-3-trimethylsilyloxy-1,3-butadiene **412**, otherwise known as Danishefsky's Diene (Scheme 4-5).[61] Cycloadditions of this diene proceed even with relatively unactivated dienophiles with good regioselectivity, due to the synergism of the two oxygen atoms. The addition of **412** to the relatively unreactive dienophile **413** afforded **414**, a valuable intermediate in the synthesis of vernolepin.[62]

Scheme 4-5

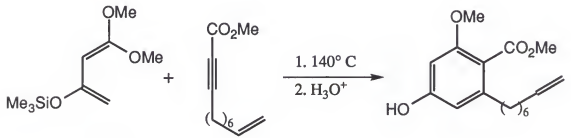


412 **413** **414**

Of great interest to our study was the use of the related 1,1-dimethoxy-3-trimethyl-silyloxybutadiene **415** with

alkynic dienophiles.[63] Despite the trisubstitution of the diene, the reaction proceeded rapidly, and after treatment with aqueous acid, led to polysubstituted phenols (Scheme 4-6), clearly demonstrating that the electronic advantage of the oxygens can overcome the steric requirements.

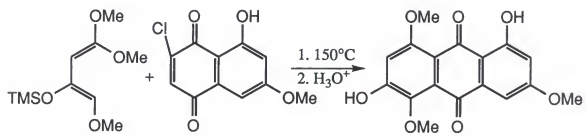
Scheme 4-6



415 **416** **417**

Scheme 4-7 shows that even tetrasubstituted dienes such as **418** undergo cycloaddition to *p*-quinones, thereby opening a convenient route to polyoxygenated anthraquinone pigments such as **420**.[64]

Scheme 4-7

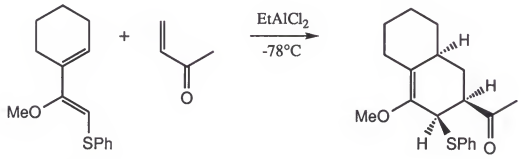


418 **419** **420**

Sulfur-Substituted Dienes

Sulfur-substituted dienes generally show an enhanced reactivity in Diels-Alder reactions compared to their oxygen analogs[65] In a competition between sulfur- and oxygen-substituents, the sulfur directing effect predominates. (Z)-2-Methoxy-1-(phenylthio)-1,3-butadienes **(421)** react with methyl vinyl ketone (Scheme 4-8), affording exclusively the *endo* adduct **422** in which the regiochemistry is completely controlled by the sulfur despite the juxtaposed effect of the oxygen substituent.[66]

Scheme 4-8

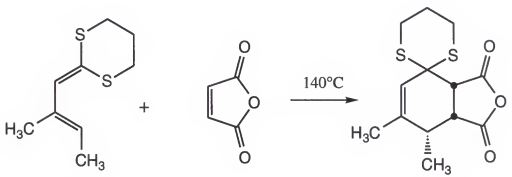


421 **422**

Another less frequent application of sulfur-substituted dienes involves vinylketene thioacetals, accessible through Peterson olefination of α,β-unsaturated aldehydes and ketones.[67] Despite the increased electronic effect of the sulfur over oxygen, the increased steric demand of vinylketene thioacetals render them quite unreactive in

Diels-Alder reactions. However, there are reports in the literature of successful applications of such systems in Diels-Alder reactions. Scheme 4-9 shows the reaction of a bis[sulfur]-substituted butadiene with maleic anhydride.[68] Other methods for the synthesis of such dienes have been developed but will not be part of this review, as they do not pertain to the current study.[69]

Scheme 4-9



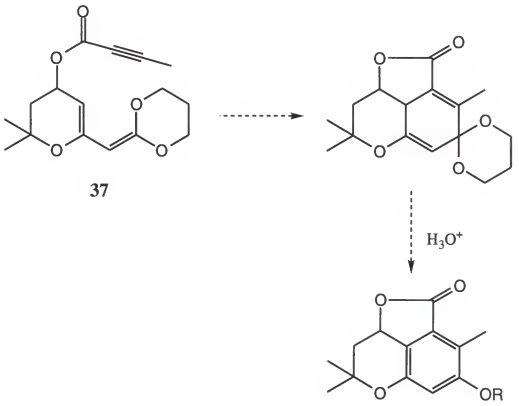
423 **424**

Applications to Pyranocoumarins

As discussed in Chapter 3, a variety of heterodienes for use in the construction of pyranocoumarins were prepared. In order to expand the scope of the method, several retrosynthetic approaches, leading to both linear as well as angular systems will be examined. Scheme 4-10 shows our initial approach to angular pyranocoumarins involving the synthesis of an O,O-ketene acetal-substituted diene **(37)**.

This will allow the introduction of an oxygen substituent required in the product, and still allow elimination of the other oxygen which will lead to the aromatization of the adduct.

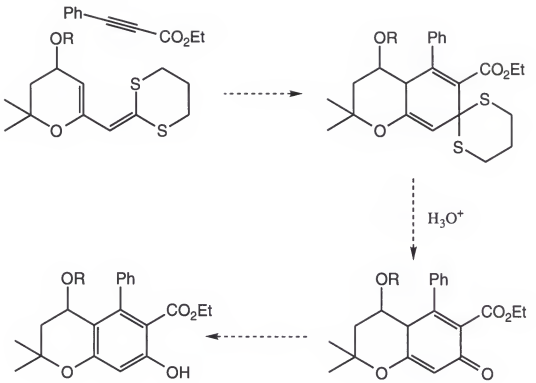
Scheme 4-10



37

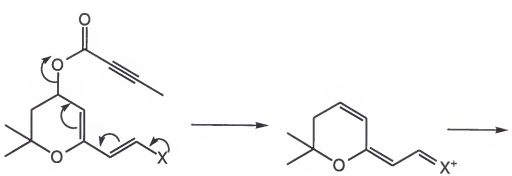
An alternate method that allows both the oxygenation of the aromatic ring as well as the aromatization process involves the use of a vinylketene thioacetal, shown in Scheme 4-11. Subsequent treatment with mercuric acetate affords the ketone analog which exists in its tautomeric form as the phenol.

Scheme 4-11



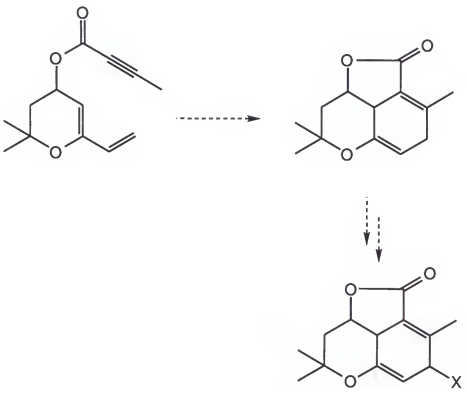
In addition to the obvious steric disadvantage of the oxygen and sulfur substituents, of great concern is also the pathway shown in Scheme 4-12 which can lead to the elimination of the dienophile subunit to a new triene.

Scheme 4-12



A potential solution to this problem, while clearly reducing the scope of our synthesis is the construction of an unsubstituted analog, as shown in Scheme 4-13. This will leave the relatively difficult problem of functionalizing that position in a later step.

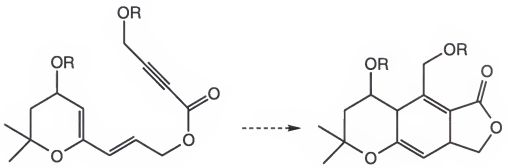
Scheme 4-13



The construction of linear pyranocoumarins requires a different approach shown in Scheme 4-14. This approach differs from the synthetic plans presented for angular systems in the linkage between the diene and the dienophile component. As opposed to the angular systems, the adducts

formed in this approach will require further manipulations to install the required oxygen functionality.

Scheme 4-14

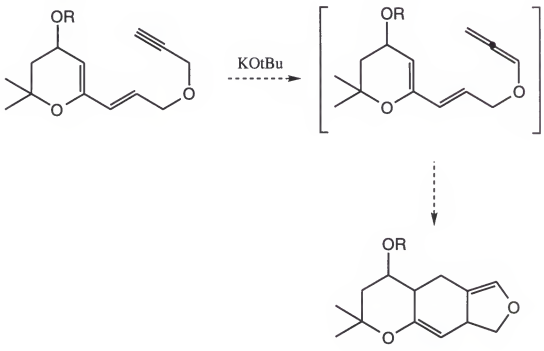


One limitation of the four approaches discussed above is the nature of the linkage between the diene and the dienophile. As pointed out by Boeckman,[70] ester linkages are not ideal for intramolecular Diels-Alder reactions. Boeckman attributes the low reactivity of such systems to poor overlap of the non-bonding electrons of the ethereal oxygen and the carbonyl group in the transition state

One obvious alternative to this potential problem is the construction of the propargyl ether analog, as shown in Scheme 4-15. Treatment with potassium t-butoxide will generate the allene which has been shown to undergo similar Diels-Alder reactions, as discussed in Chapter 2. Functionalization of the *exo-olefin* will require only one additional transformation and therefore does not enhance the complexity of the route. Another advantage of this approach lies in the fact that allenes generally undergo

cycloadditions at lower temperatures than their alkynyl analogs.

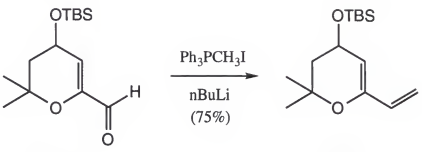
Scheme 4-15



Results and Discussion

With aldehyde **31** in hand, we first carried out the synthesis of the unsubstituted diene **38** (Scheme 4-16). As expected, this diene system proved to be quite stable, even under mild acidic conditions (e.g. silica gel). The ^{1}H NMR exhibited a characteristic pattern for a terminal olefin, with J = 11 Hz (*cis* coupling), and J = 17 Hz (*trans* coupling). ^{13}C NMR confirmed the presence of two new vinyl signals at 104.5 and 133.0 ppm, respectively.

Scheme 4-16

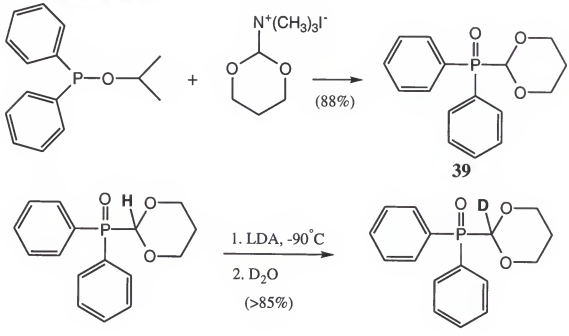


31 **38**

Despite the fact that the synthesis of **38** proceeded with no difficulty even on large scale and the relatively easy purification procedure, an efficient synthesis of pyranocoumarins required the functionalization of the diene terminus. Ideally, as described previously, we required a ketene O,O-acetal-substituted diene. In order to achieve such a transformation with an acid-sensitive aldehyde such as **31**, an alternate procedure using basic conditions had to be developed. Our approach consisted of a Horner-Wittig diphenyl phosphinoyl anion reagent, shown in Scheme 4-17. A method for the synthesis of the protonated form of the anion has previously been described and involves the Arbuzov reaction of isopropyl diphenylphosphinite with (1,3-dioxan-2-yl)-trimethylammonium iodide.[71a] The ammonium salt was easily prepared by quaternization of the tertiary amine analog with ethyl iodide while the isopropyl diphenylphosphinite was prepared by the reaction of chlorodiphenylphosphine with freshly prepared sodium isopropoxide. The reaction proceeded

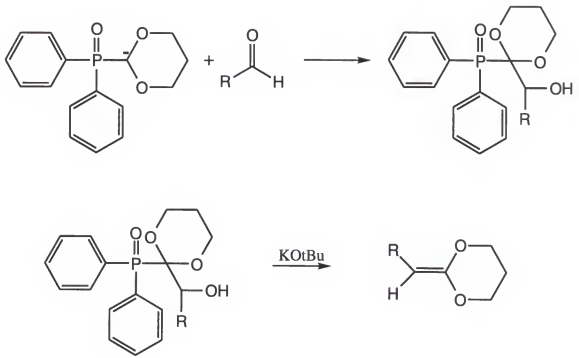
quite readily and generated **39** in excellent yield as a white solid. The ^{1}H NMR was consistent with the formation of **39**, showing the expected pattern for the protons α to the phosphorous, with J_{H-P} =1.5 Hz and J_{H-H} = 6Hz. The ^{13}C NMR was even more characteristic with J_{C-P} ranging from 10 to 140 Hz, depending on the distance of the carbon to the phosphorous. With **39** in hand, we attempted a deprotonation/reprotonation experiment using lithium diisopropyl amide at -95°C, folowed by addition of D_2O at various temperatures (Scheme 4-17). We observed that when D_2O was added at -95°C, the deuterated analog of **39** was observed as the only product. However, if the mixture of base and diphenylphosphinite was allowed to warm to even -60°C, significant decomposition was observed.

Scheme 4-17



This observation clearly indicated the limitation of the reagent to aldehydes reactive enough to undergo the transformation at low temperatures. In addition, such reactions will be expected to form the alcohol derivative and require further treatment with base in a subsequent step in order to generate the desired alkene product, as shown in Scheme 4-18. Evidence for this alcohol was observed when 1-naphtaldehyde was treated with the phosphine oxide anion. However, isolation of this alcohol was difficult due to its relatively low stability.

Scheme 4-18

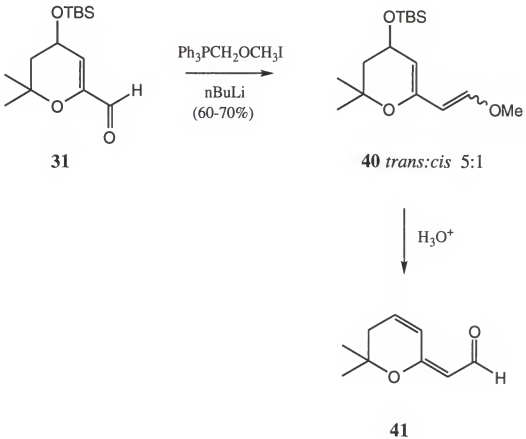


We attempted the coupling of **39** with **31** under the established conditions (e.g. temperatures lower than -90°C in

order to avoid decomposition of **39**), but isolated unreacted starting materials from the reaction. In order to fully understand the reactivity of our aldehyde with Horner-Wittig-type reagents, we attempted the preparation of the more-common methyl enol ether analog **40**, using the methoxymethyl diphenylphsphine oxide carbanion, but found that even at room temperature the aldehyde was isolated intact even after several days of reaction. However, when the same reaction was attempted using methoxymethyl triphenyl phosphine iodide and nBuLi, the reaction proceeded readily at 0°C in satisfactory yields, resulting in the formation of **40** as a mixture of geometric isomers in a 5:1 *trans:cis* ratio (Scheme 4-19). The stereochemistry was assigned based on the proton coupling constants (J = 9 Hz for *cis* and J = 11 Hz for *trans*). The ^{13}C NMR showed the expected change from **38**, where the methylene vinyl carbon exhibited a chemical shift of 104.5 ppm. The equivalent carbon in the methoxyvinyl analog is shifted downfield to 127.2 ppm by the oxygen substituent. While purification via flash chromatography was feasible on small scale using neutral alumina as the stationary phase, on larger scale, significant amounts of aldehyde **41** were observed by the appearance of an aldehyde signal as a doublet in the ^{1}H NMR. This process was favored dramatically during purification using silica gel and is presumed to be an acid catalyzed hydrolysis of the labile methyl enol ether functionality. The process using the normal Wittig reaction was found to be satisfactory on small scale reactions and

careful purification using deactivated silica gel did indeed afford **40** with satisfactory purity to be used in a subsequent transformation.

Scheme 4-19



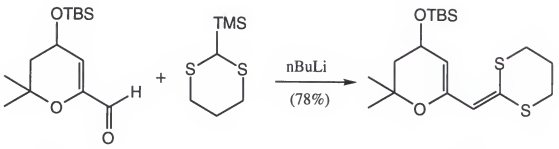
31 **40** *trans:cis* 5:1

41

The preparation of the methyl enol ether-diene **40** allowed us to draw essential conclusions about the preparation of the O,O-vinylketene acetal analog. The fact that the Horner-Wittig reaction using the methoxymethyl reagent was not successful indicated a limitation of this system and brought additional evidence that supported our

assumption that aldehyde **31** was not an ideal candidate for reaction with carbanions derived from phosphine oxides. In addition, the relatively low stability of the methyl enol ether moiety to even mildly acidic conditions pointed to another limitation for use in Diels-Alder reactions which often require high temperatures or acid catalysis. We therefore turned our attention to the preparation of the ketene thioacetal analog using an established procedure based on the Peterson olefination. The reaction of aldehyde **31** with 2-lithio-2-trimethylsilyl-1,3-dithiane afforded the expected ketene thioacetal in good yield, as shown in Scheme 4-20. The ^{1}H NMR displayed the expected pattern, with a singlet at 6.0 ppm indicative of the presence of a proton at C2 of the butadiene system formed. The ^{13}C NMR confirmed the formation of the new olefin by the presence of four vinyl signals at 149, 134, 122, and 104 ppm, respectively.

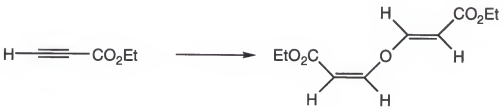
Scheme 4-20



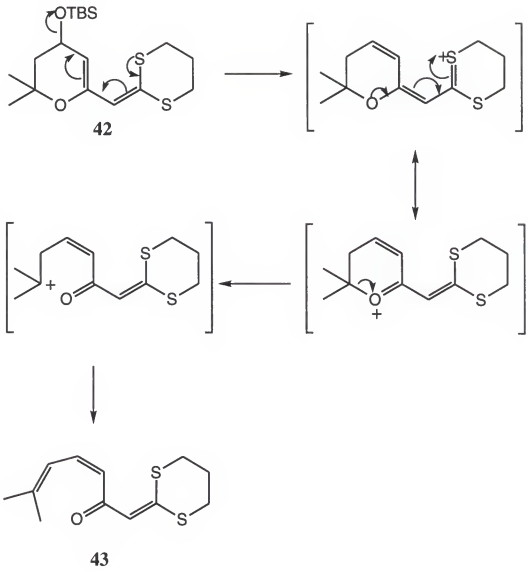
31 **42**

An intermolecular Diels-Alder was attempted using Ethyl propynoate, but it was found that under the reaction conditions, ethyl propynoate undergoes dimerization, as shown in Scheme 4-21. In order to avoid this problem, 3-phenyl ethyl propynoate was used. However, due to the steric constraints imposed by not only the large dithianylidine substituent on the diene, as well as the phenyl substituent on the dienophile, the cyclization proceeded in a sluggish manner at lower temperature, giving complex mixtures of adducts. The mixture was separated using preparative thin layer chromatography and afforded trace amounts of adducts containing aromatic signals in the ^{1}H NMR. At higher temperatures, the reaction yielded a single product resulting from the ring-opening reaction of the diene system, as shown in Scheme 4-22. The *cis* geometry of the central olefin unit in **43** was assigned by the J = 12 Hz coupling constant. The ^{13}C NMR confirmed the formation of the ketone with a chemical shift of 187 ppm for the carbonyl carbon.

Scheme 4-21



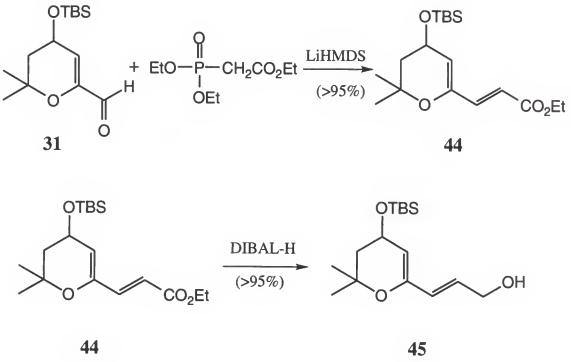
Scheme 4-22



As described earlier, we attempted the construction of triene systems for the synthesis of linear pyranocoumarins. The linkage between the diene and the dienophile required for the synthesis is at the exocyclic terminus of the butadiene system and can also be prepared from the same aldehyde **31**.

Scheme 4-23 shown our approach to such systems. Reaction of **31** with triethylphosphonoacetate proceeded very cleanly affording the *trans*-olefin of the α,β-unsaturated ester **44** as the only observed product. A trace amount (less than 4%) *cis*-olefin was formed during one attempt and was used to confirm the geometry of the *trans*-product (J = 15 Hz for the major isomer and J = 11 Hz for the minor isomer, presumed to be *cis*). The ^{13}C NMR of **44** also exhibited the normal pattern, with two new vinyl signals at 118 and 140 ppm and a new carbonyl signal at 167 ppm. Reduction of **44** with DIBAL-H proceeded cleanly and afforded allylic alcohol **45** in almost quantitative yield.

Scheme 4-23



Due to the efficiency of the reduction process, purification of **45** was not necessary. However, when a small sample was purified for elemental analysis using flash chromatography with silica gel as the stationary phase, we observed the formation of a new product drastically different from **45**, along with the recovery of purified **45**. We attributed the formation of this product to the acidic conditions of the purification and attempted to establish conditions for the controlled synthesis of the rearrangement product. We later found that a pure sample of **45** left in $CDCl_3$ for one week is also rearranged to the same product.

Several acidic conditions were attempted, including dilute HCl in methanol, lithium perchlorate in ether and triethylamine hydrochloride in ether. While all these conditions generated some of the rearranged product, triethylamine hydrochloride converted **45** to the rearrangement product in better than 80% yield. The characterization of the product was not trivial, requiring advanced 2-D NMR experiments using a high-field 500 MHz instrument. A superficial investigation of the ^1H NMR identified some key features of the structure. Most strikingly, the *gem*-dimethyl signal was a singlet, indicating the absence of a chiral center in the vicinity. The absence of a signal from 2.8 ppm to 5.8 ppm clearly indicated the absence of an α-oxygen proton, while the absence of the *tert*-butyl signal at 0.9 ppm and the *gem*-dimethyl signal at 0.1 ppm indicated the loss of the t-butyl dimethyl silyl group. The vinyl region indicated

the presence of five vinyl signals, some with unusually small coupling constants of 1.5 to 3.4 Hz). The presence of a vinyl signal at 7.4 ppm pointed to the formation of an aromatic-type system. Our assumptions derived from the ^{1}H NMR were further confirmed by the ^{13}C spectrum, where six vinyl signals were observed, along with three alkyl signals. An APT experiment was performed and showed that five of the six vinyls were methyne carbons, while only one was a quaternary carbon. High resolution mass spectroscopy using chemical ionization indicated the formal loss of t-butyl dimethyl silyl alcohol from **45**. The preliminary spectral information led to the conclusion that the structure of the rearranged product must be quite different from the structure of **45**.

Advanced experiments were performed using a Unity-500MHz instrument, starting with Nuclear Overhauser Effect (NOE) difference experiments, which allowed us to establish connectivity hydrogens on adjacent or neighboring carbons. The conclusion of the NOE experiments is shown in Scheme 4-24. While this only established approximately one-half of the molecule, used in combination with the high resolution mass spectral data, it enabled us to make some assumptions which allowed the design of other NMR experiments.

Heteronuclear multiple quantum coherence (HMQC) experiments, along with heteronuclear multiple bond correlation (HMBC) experiments allowed us to further establish the connectivity and along with the NOE-established connectivities led to the proposal of the structure shown in

Scheme 4-25.[71b] Figure 3 contains quantitative results from the NOE experiments. Of great interest is the NOE observed for the furan proton H_C when the external methylene subunit was irradiated, not only establishing the *cis*-geometry of the olefin, but also offering insight into the conformation of the molecule. The most convincing evidence relating to the assigned structure was obtained from the MNBC spectrum, which offers indirect detection of C-H connectivity and proximity two or even three bonds away.

Scheme 4-24

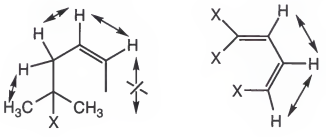
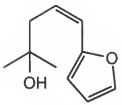


Figure 4 contains the results obtained from HMBC, along with the full assignment for the frequencies of all carbon and proton signals. Noteworthy is the HMBC connectivity between the furan carbon at 153.1 ppm and the protons in the furan ring, as well as in the *cis*-olefin connected to the furan ring. COSY and long-range COSY experiments further confirmed the *cis*-geometry of the external olefin.

Scheme 4-25



46

The structure is in agreement with the ^1H NMR data in that it rationalizes the observation of the presence of an alcohol proton with no corresponding α-hydroxy signal. In addition, the molecular formula $C_{10}H_{14}O_2$, determined by high resolution mass spectroscopy, indicated the presence of a ring system. The two apparently conflicting observations are nicely reconciled by the opening of the pyran ring and the formation of a tertiary alcohol, along with the formation of a new furan ring.

Mechanistically, the formation of **46** can be rationalized along the lines of previous rearrangements observed with pyranyl systems and described in this report. Scheme 4-26 describes one possible mechanism, while other similar mechanisms can be drawn and have not been excluded. In order to further elucidate the mechanism, we prepared a deuterated analog of **45**, as shown in Scheme 4-27. The analog was expected to diferentiate between a hydride shift of H_a and a simple proton abstraction. In the case of a hydride shift mechanism, it was expected that two of the hydrogens in the furan ring of **46** would be replaced by deuterium. Loss of H_2O

would compete with loss of HOD in the final step leading to the formation of the furan and at least some of the H_b in the furan ring would be replaced by deuterium. In the case of the simple deprotonation mechanism, deuterium incorporation would only be expected at H_1. As illustrated in Scheme 4-27, the deuterium was not incorporated in place of H_b, therefore suggesting a deprotonation mechanism, and not a hydride shift.

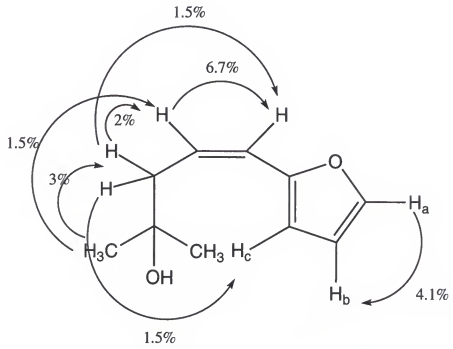


Figure 3: Quantitative NOE results for **46**

While **46** was not part of the goal of this synthesis, the fortuitous observation of its formation further expand the scope of the project to the synthesis of monoterpenes, as the structure of **46** is very similar to common monoterpenes.

With **45** in hand, we proceeded to the construction of the proposed triene systems (Scheme 4-28). Esterification with commercially available acetylinic acids afforded esters **47** and **48**. The formation of such esters was confirmed mainly by high resolution mass spectroscopy, as the NMR spectra would be difficult to distinguish from the spectra of a mixture of acid and alcohol starting materials. However, the allylic signals in the ^{1}H NMR did indeed resolve from a broad doublet in the alcohol to a clean, sharp doublet in the ester, due to the removal of the hydroxyl proton. The formation of the ester also shifted the allylic signal downfield by 0.4 ppm to 4.8 ppm, due to the shielding effect of the electron withdrawing ester group.

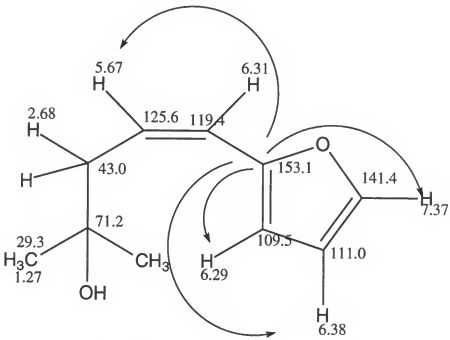
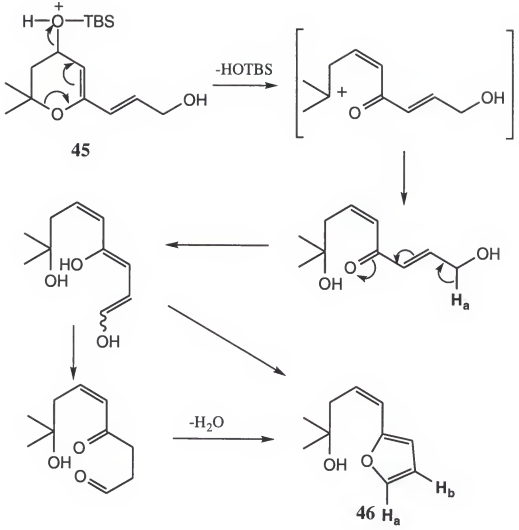


Figure 4: HMBC results for **46**

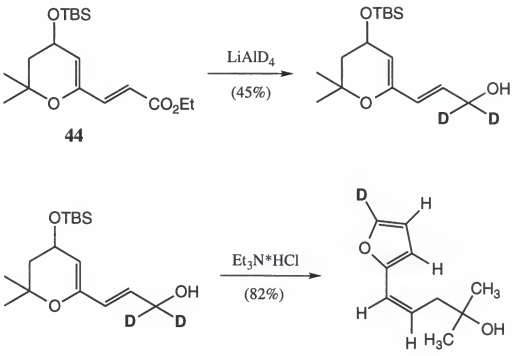
Scheme 4-26



In order to increase the functionality of the triene system we prepared a more functionalized butynoic acid. The synthesis of 4-(t-butyl dimethysiloxy)-butynoic acid **49** is presented in Scheme 4-29. Esterification of this acid with alcohol **45** allowed the construction of a highly functionalized triene system, which upon cyclization would

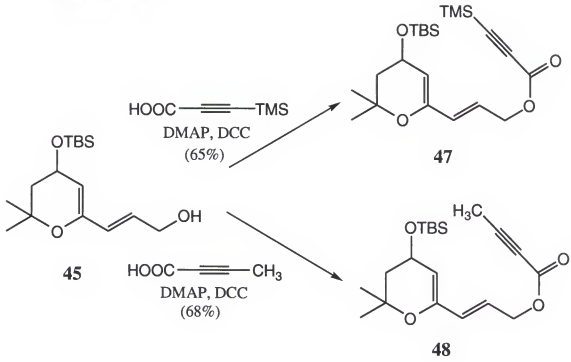
afford a pyranocoumarin backbone with all the requisite functionality in place.

Scheme 4-27

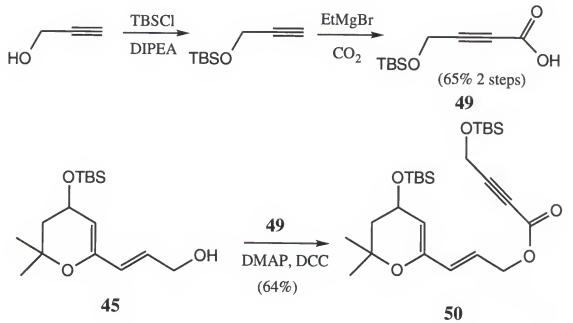


To our disappointment, neither triene system afforded proved to be a good candidate for intramolecular cycloaddition. Heating of **47**, **48**, or **50** afforded complex reaction mixtures. The NMR data indicated loss of the OTBS group at temperatures higher than 140°C, with the appearance of new vinyl signals, possibly corresponding to a new triene system resulting from elimination, or to a complex mixture of cycloadducts.

Scheme 4-28

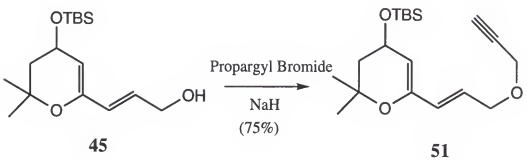


Scheme 4-29



As discussed earlier, an alternate route to the activation of an acetylinic dienophile is the *in-situ* generation of the corresponding allene which generally undergoes facile Diels-Alder reactions even in the case of unactivated dienophiles. Treatment of alcohol **45** with propargyl bromide in the presence of sodium hydride afforded propargyl ether **51** (Scheme 4-30) in good yield. Treatment of ether **51** with potassium t-butoxide did not generate the expected product or observable amounts of allenyl intermediates.

Scheme 4-30



45 **51**

Conclusion

Starting with intermediate aldehyde **31**, we have developed routes to a new class of heterodienes that can be used in the construction of pyranocoumarins. On a broader scope, the methodology presented herein can be applied to other pyran-containing natural products. While these diene and triene systems can be generated in excellent yields by

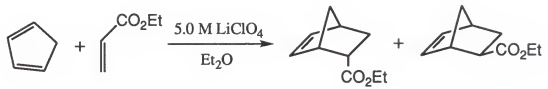
convenient methods on small to medium scale, they exhibit a low level of stability. The facile acid-catalyzed ring-opening which most of the dienes described undergo limits the scope of the method. However, with careful choice of conditions these dienes can have limited use in the construction of pyran-containing natural products. Although the thermal studies presented herein have not identified proper conditions to effect cyclization, we believe that careful selection of temperature and solvents can lead to successful cyclizations. Furthermore, some of the rearrangement products can be used in the synthesis of different classes of natural products, such as monoterpenes.

CHAPTER 5
TRANSFORMATIONS IN HIGHLY POLAR ORGANIC MEDIA

Introduction

Recent reports have revealed that an ethereal solution of lithium perchlorate in diethyl ether is an astounding medium for a wide variety of reactions. While studies relating to the effects of polar organic media on typical organic reactions have been published[72] for quite some time from a theoretical standpoint, only recently has the use of such media been applied to organic synthesis.[73-80] One of the earlier reports come from Sauer,[73] who was the first to recommend such media for Diels-Alder reactions. In 1990, Grieco[74] carried out Diels-Alder studies using cyclopentadiene and ethyl acrylate and demonstrated that the reactions proceeded with increased rates and improved endo-selectivity in a 5.0 M solution of lithium perchlorate in diethyl ether, compared to an aqueous reaction medium (Scheme 5-1). Grieco explained the accelerating effect in analogy to the effects observed with aqueous systems, attributing the increase in rate to hydrophobic or "internal pressure" effects on the reactants encapsulated in "solvent cavities".

Scheme 5-1

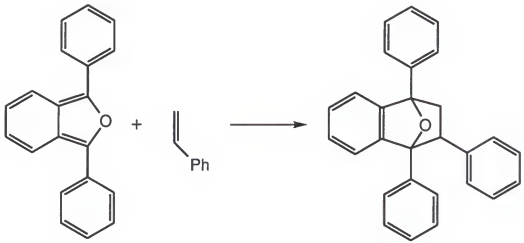


8 : 1

However, Dailey[75] showed in a later report that Li^+ is functioning as a Lewis acid, complexing with the dienophile. His conclusion was initially based on the observation of a Diels-Alder reaction that is not accelerated by lithium perchlorate versus water. If the rate enhancement was indeed due to an "internal pressure" effect as stated by Grieco, then Dailey assumed that the rates of all Diels-Alder reactions should be accelerated since all Diels-Alder reactions proceed with a highly negative volume of activation. The reaction of 1,3-diphenylisobenzofuran with styrene was indeed found to be unaffected by lithium perchlorate (Scheme 5-2). Therefore, the next step in Dailey's study was to assess the Lewis acidity of lithium perchlorate. If lithium perchlorate is functioning as a Lewis acid in some Diels-Alder reactions, then the second order rate constant should depend on the lithium ion concentration. Dailey measured the second-order rate constants for the Diels-Alder reaction between acrylonitrile and 9,10-dimethylanthracene in the presence of various concentrations of lithium perchlorate. The reactions were carried out at

28°C in ether under large excess of dienophile and monitored by UV spectroscopy. In 4.5 M lithium perchlorate in diethyl ether, the rate enhancement is a factor of 9 over the purely thermal reaction. The linear correlation (rate vs. concentration of perchlorate) indicates that there is a first-order dependence on the concentration of lithium perchlorate. This observation is further supported by the previous reports indicating that enhanced endo-selectivity is typically observed in most Lewis acid catalyzed Diels-Alder reactions, a fact also observed with lithium perchlorate.

Scheme 5-2

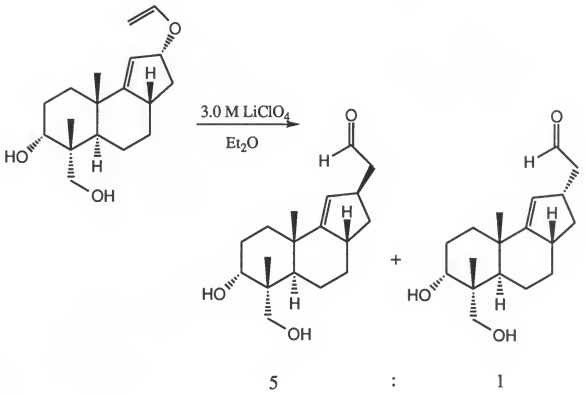


A recent report by Kumar,[76] however, supports Grieco's theory and reconciles it with Dailey's observation of unaffected cycloadditions. According to Kumar, the Lewis acidity of Li^+ is strong only in the gas phase, and NMR experiments, as well as MNDO calculations show that the

acidity is considerably moderated by diethyl ether as a solvent. Kumar maintains that the reasons of ineffective role of internal pressure need to be examined in the context of the magnitude of activation volumes. His report uses theoretical calculations relating to the internal pressure of various solvents to support this theory.

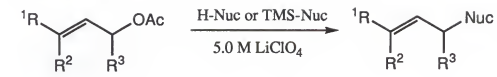
While having similar properties with aqueous systems, ethereal lithium perchlorate is superior to aqueous media due to its compatibility with substances sensitive to hydrolysis. Reactions which normally take place under vigorous conditions have been found to proceed smoothly under mild conditions at room temperature using lithium perchlorate. For example, allyl vinyl ethers have been found to undergo unprecedented [1,3] sigmatropic rearrangement at room temperature using 3.0 M lithium perchlorate (Scheme 5-3).[77] This finding in is contrast with previous studies by the same authors showing the same vinyl ether to undergo exclusive [3,3] sigmatropic rearrangement at 80°C in water-methanol. The [1,3] sigmatropic rearrangement of other allyl vinyl ethers was reported with good to excellent yields. It was found that the concentration of lithium perchlorate has a dramatic effect on the rate of reaction. For the purpose of our study, it is important to note that the [1,3] sigmatropic rearrangement product was usually accompanied by small amounts of diene resulting from an elimination process.

Scheme 5-3



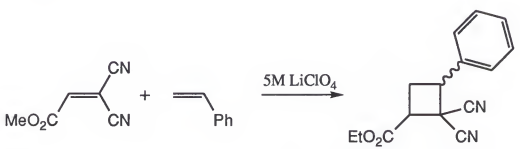
Pearson and co-workers[78] found that allylic acetates and allylic alcohols can undergo substitution reactions in perchlorate solution (Scheme 5-4). The findings were particularly useful due to the wide range of nucleophiles which can be used. Initially, Pearson used conventional carbon nucleophiles such as indoles and silyl enol ethers, but later found that the application can be extended to electron-rich π-bonds such as ketene acetals and allyl- or propargyltrimethylsilane. The fact that these transformations are limited to allylic systems and are favored by high degrees of substitution at the allylic position indicate the formation of a carbocation as an intermediate.

Scheme 5-4



Another report by Hall and co-workers[79] involves the use of lithium perchlorate in [2+2] cycloadditions. Under thermal conditions, olefins with two cyano groups on the same sp^2 carbon and an ester substituent on the other sp^2 carbon undergo inverse electron demand [4+2] cycloaddition with phenyl vinyl sulfide, generating dihydropyran products. However, when lithium perchlorate is employed as a medium, the cyclobutanes are isolated as the only product from the reaction with styrene (Scheme 5-5).

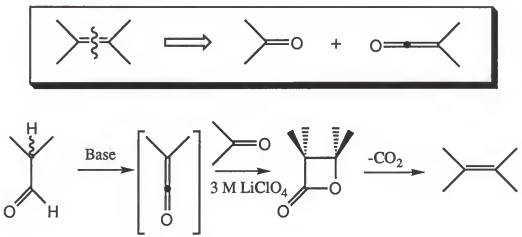
Scheme 5-5



An application of [2+2] cycloadditions is the reaction of ketenes with carbonyl compounds generating olefins reported by Cossio and Arrastia (Scheme 5-6).[80] The reaction

represents a viable alternative to the Wittig and Peterson olefination, proceeding at room temperature in excellent yields.

Scheme 5-6



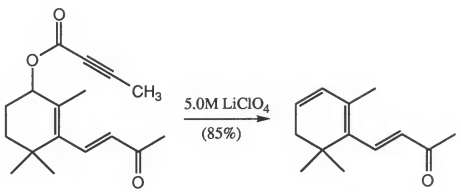
The goal of the present report is the investigation of the effect of lithium perchlorate on pyran diene and triene systems in intramolecular Diels-Alder reactions. However, due to the high degree of functionality of our systems initial studies were required to explore the compatibility of this polar medium with a wide variety of functional groups.

Results and Discussion

The first investigation involved diene system **4** which undergoes thermal intramolecular Diels-Alder reactions in good yield. The triene was dissolved in a freshly prepared

5.0 M lithium perchlorate solution in ether. After eight hours, thin layer chromatography showed no triene starting material present. However, ^{1}H NMR studies showed that the product was not the cycloaddition adduct. High resolution mass spectroscopy indicated formal loss of butynoic acid from the molecular weight of the starting material. The ^{1}H NMR did not seem to be consistent with the elimination product but showed the (E)-but-1-ene-2-one substituent on the cyclohexane ring intact. The signal at 5.3 ppm corresponding to the α-ethereal oxygen-proton disappeared and a new singlet appeared at 5.8 ppm, integrating for two protons. While the integration pattern and chemical shift was indeed consistent with an elimination product, the multiplicity of the signal was not. If indeed the elimination product was formed, a pair of doublets should be observed. ^{13}C NMR, however, confirmed the presence of six vinyl carbons and HETCOR experiments showed that the singlet at 5.8 ppm in the ^{1}H NMR corresponded to two protons on two different carbons. We therefore assumed that the elimination product was formed and that the singlet at 5.8 ppm is due to the fact that the two new vinyl protons fortuitously have the same chemical shift. In order to confirmed our assumption, NOE experiments were performed and confirmed the proposed structure as shown in Scheme 5-7.

Scheme 5-7

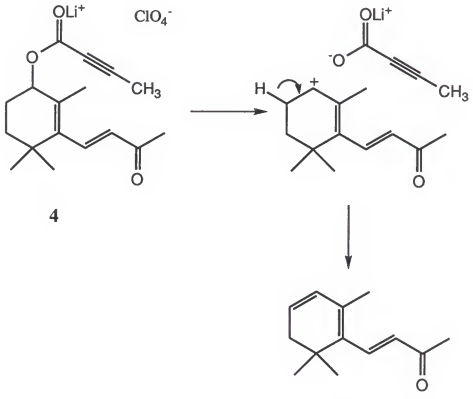


4 **52**

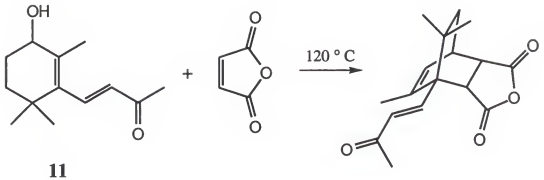
The formation of the elimination product, while surprising at the time, can be explained based on several previous observation. As discussed in the introduction, allylic acetates are known to undergo nucleophilic substitution reactions in lithium perchlorate, presumably through the formation of an allyl carbocation. If such a carbocation is formed in the absence of a nucleophile, elimination becomes a viable path of reaction. Scheme 5-8 shows a possible mechanism for this transformation. The formation of an intimate ion pair is a proposed intermediate. Alternatively, the reaction could proceed directly via a [3,3] sigmatropic rearrangement-type internal abstraction of a proton by the ester carbonyl. In the case of the ion pair, elimination via an E1-type mechanism affords the triene product. In a related study[36] previously done in our group, Dr. Radi Awartani observed that if alcohol **11** is heated with maleic anhydride at 120°C, a Diels-Alder adduct is observed

(Scheme 5-9). The adduct however is not the expected adduct formed from the reaction of the diene present in the starting alcohol **11** and maleic anhydride, but instead is due to the formation of the same elimination product **52** as an intermediate. The cyclohexadiene system then acts as a diene and reacts in the Diels-Alder reaction.

Scheme 5-8



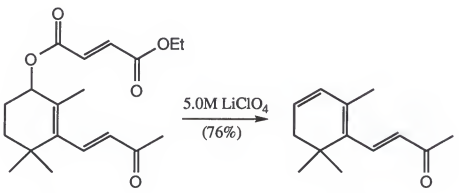
Scheme 5-9



11

In order to determine whether the nature of the ester would have an effect on the outcome of the perchlorate elimination, we attempted eliminations with analogs of **4** containing different dienophile components. Fumarate ester **12** was used in such a study and gave the same product as **4**, with only slightly longer reaction times and somewhat lower yields, as shown in Scheme 5-10.

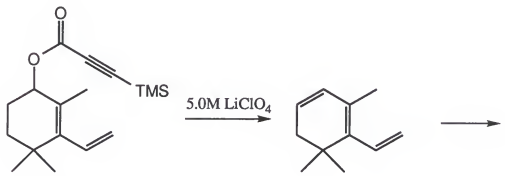
Scheme 5-10



12 **52**

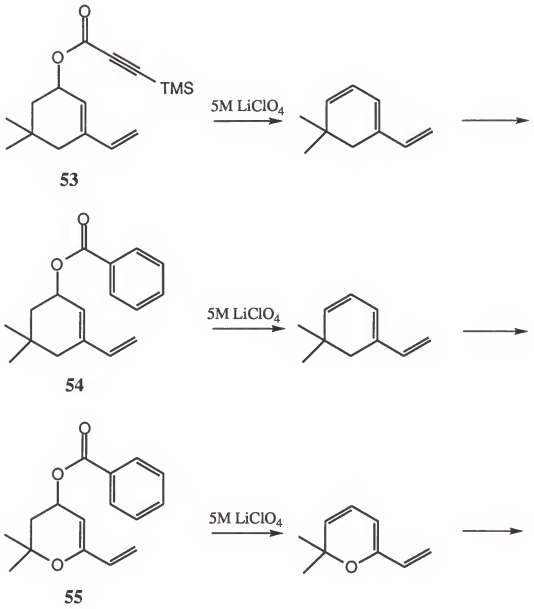
Attempts to carry out eliminations using vinyl-cyclohexene-containing trienes pointed out a limitation of this process. As previously noted with styrene,[79] lithium perchlorate is an adequate medium for some polymerization processes, and our results seem to indicate that a similar process must take place for vinyl-cyclohexadienes. For example, the elimination using **10** as a starting material resulted in the consumption of the starting material and the recovery of an insoluble residue. Crude ^{1}H NMR spectra of the reaction indicated the presence of a pair of new vinyl signals consistent with the formation of an elimination product, as shown in Scheme 5-11. Other attempts to form vinyl-cyclohexadienes are summarized in Scheme 5-12 and gave similar experimental observations. The author is indebted to Ms. Patricia Bottari for her generous donation of **53** and **60**.

Scheme 5-11



10

Scheme 5-12

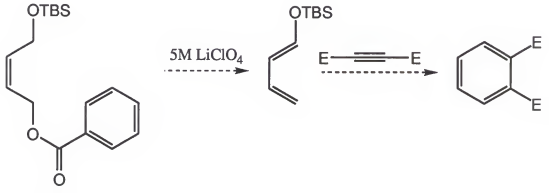


53 **54** **55**

In an attempt to develop a practical application that would take advantage of the properties of lithium perchlorate, we investigated the possibility of a tandem elimination, generating a diene *in-situ*, followed by a Diels-Alder reaction which could be catalyzed by the reaction

medium. Previous reports have shown that Diels-Alder reactions of oxygen-substituted butadiene proceed very well in lithium perchlorate.[74] Therefore, we embarked on the synthesis of **57**. Treatment of **57** with lithium perchlorate would result in the elimination of the allylic benzoate and the formation of a substituted butadiene (Scheme 5-13). If the reaction is carried out in the presence of dimethylacetylene dicarboxylate, an adduct could be generated.

Scheme 5-13

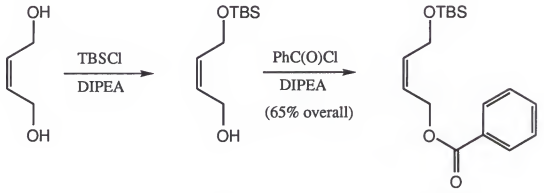


57

The synthesis of **57** was carried out using (E) 2-butene diol as the starting material (Scheme 5-14). Treatment with one equivalent of t-butyl dimethylsilyl chloride generated **56** in excellent yield. Careful treatment of **56** with benzoyl chloride formed the expected benzoate ester **57**. Surprisingly we found purification of **57** to be very tedious due to the difficulty of removing unreacted benzoyl chloride. Our

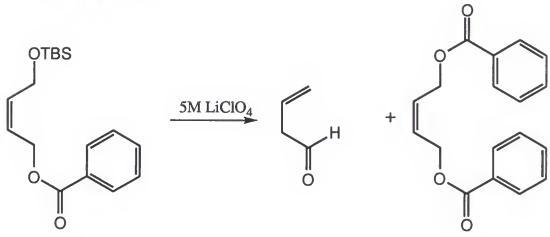
observations showed that even small amounts of benzoyl chloride greatly hindered the perchlorate elimination.

Scheme 5-14



56 **57**

Scheme 5-15

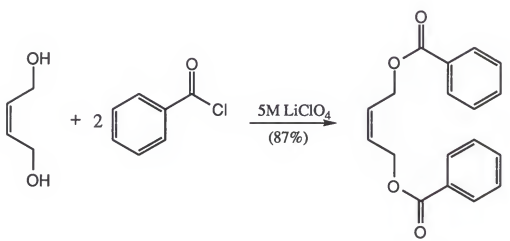


57 **58** **59**

With **57** in hand, we proceeded with the elimination reaction and observed the formation of aldehyde **58** (Scheme 5-15), which proved to be difficult to isolate in good yield due to its high volatility, along with the formation of small

amounts of dibenzoate **59**. The formation of **59** opens the question whether this medium would be effective for the formation of benzoate esters. In order to confirm our observation, cis-2-butene diol was dissolved in a 5.0 M lithium perchlorate solution and two equivalents of benzoyl chloride were added. After eight hours, the diol was consumed and the dibenzoate **59** was isolated as the major product (Scheme 5-16). Longer reaction times led to the isolation of decomposition products.

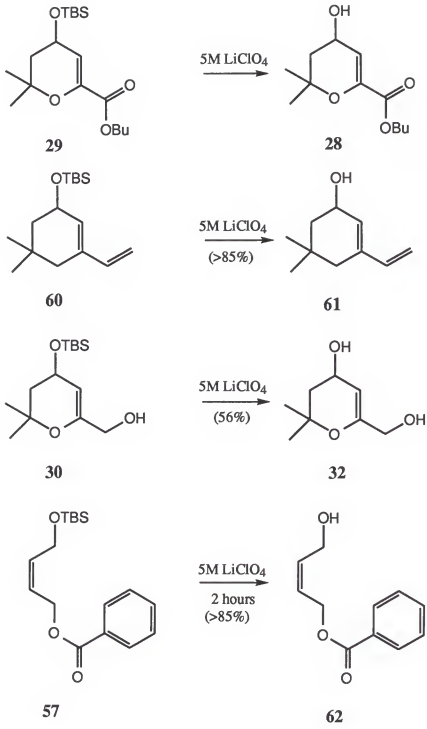
Scheme 5-16



59

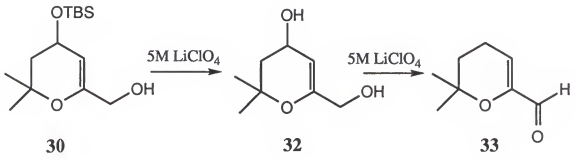
However, the formation of aldehyde **58** revealed another possible application for lithium perchlorate in the hydrolysis of t-butyl dimethylsilyl ethers. In order to explore the potential of this application, we examined the reaction of four allylic silyl enol ethers shown in Scheme 5-17. The reactions proceeded with good yields.

Scheme 5-17


OTBS
OBu
29
5M LiClO4
OH
OBu
28
OTBS
60
5M LiClO4
(>85%)
OH
61
OTBS
OH
30
5M LiClO4
(56%)
OH
OH
32
OTBS
57
5M LiClO4
2 hours
(>85%)
OH
62

Under longer reaction times, we observed the formation of other products resulting from further reaction of the resulting allylic alcohols. For example, the product of the hydrolysis of **30**, diol **32** was found to be unstable under the reaction conditions and yielded a small amount of aldehyde **33**, as shown in Scheme 5-18. The formation of aldehyde **33** has previously been observed under thermal conditions.

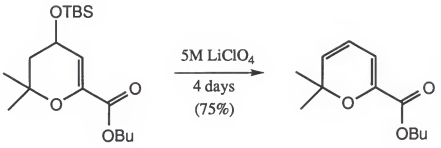
Scheme 5-18



30 **32** **33**

Another side reaction that occurs with longer reaction times was observed with **29**. While after eight to twelve hours the only product isolated was the deprotected alcohol **28**, after two days we observed the formation of diene **63** along with alcohol **28** (Scheme 5-19). After five days, the reaction afforded a 4:1 mixture of diene and alcohol, respectively. In order to further prove that this reaction is specific for alcohols, we examined the elimination using **28** as the starting material and observed the formation of the same diene **63**.

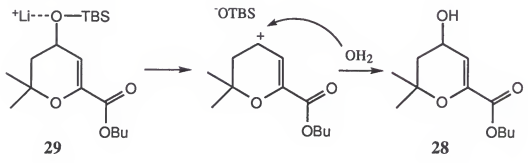
Scheme 5-19



29 **63**

Mechanistically, the hydrolysis of allyl silyl ethers can be rationalized through the formation of the same ion-pair intermediate as in the case of the elimination of esters discussed previously. Scheme 5-20 shows a possible pathway, where the carbocation formed is attacked by adventitious water leading to product, or by $TBSO^-$, reversing to starting material. The attack of $TBSO^-$ was proven in a later study involving a chiral alcohol. The elimination reaction observed with longer reaction times in the case of **29**, can be attributed to the acumulation of small amounts of perchloric acid.

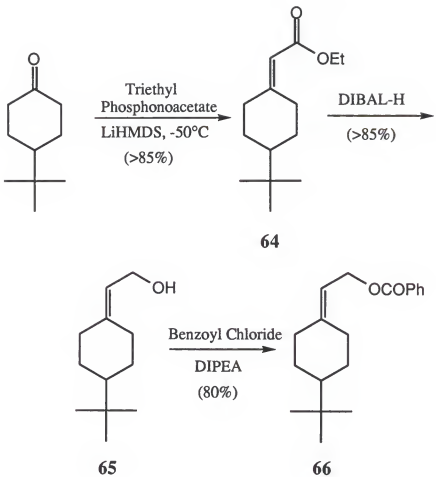
Scheme 5-20



29 **28**

The practical scope of this reaction was further explored by the synthesis of another allyl benzoate derived from t-butyl cyclohexanone. The ester, upon treatment with lithium perchlorate would afford a vinyl cyclohexene diene. Reaction of t-butyl cyclohexanone with triethyl phosphonoacetate cleanly afforded the expected α,β–unsaturated ester **64** in excellent yield (Scheme 5-21). Treatment of the ester with DIBAL-H afforded the desired allylic alcohol **65**. Esterification with benzoyl chloride allowed the formation of **66**. However, great difficulty was encountered in the purification of **66**. The unreacted benzoyl chloride which normally accompanies such reactions was found to have the same R_f value as the benzoate ester **66**. Attempts to remove all the benzoyl chloride by chromatographic methods were not successful. We also attempted to hydrolyze the benzoyl chloride using sodium bicarbonate with no success, while sodium hydroxide hydrolyzed both the benzoyl chloride, as well as the benzoate ester to afford the starting alcohol. Therefore, the elimination study using lithium perchlorate could not be performed on the benzoate ester. We attempted the elimination using the allylic alcohol, but saw only trace amounts of diene after several days of reaction, presumably due to the fact that a primary allylic carbocation must be formed, versus a secondary allylic cation in the previous example.

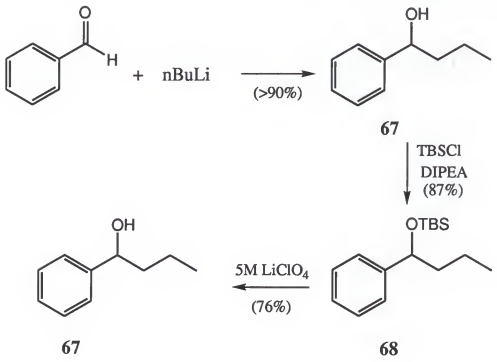
Scheme 5-21



The applicability of the hydrolysis of the silyl enol ethers was further expanded to benzylic systems (Scheme 5-22). Reaction of benzaldehyde with nBuLi afforded secondary benzylic alcohol **67** in excellent yield. Treatment of **67** with t-butyl dimethylsilyl chloride afforded **68**, which was used in the deprotection reaction. Treatment of **68** with a 5.0 M lithium perchlorate solution afforded the formation of **67** in excellent yield. Interestingly, after workup, no t-butyl

dimethylsilyl alcohol was isolated as a byproduct. This is a clear advantage over the fluoride deprotection since the silyl alcohol is difficult to remove by chromatography.

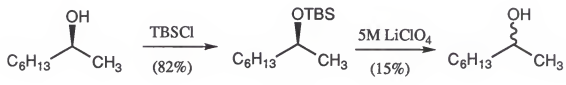
Scheme 5-22



In order to establish the formation of a carbocationic intermediate, we attempted the hydrolysis of the silyl ether of 1-octanol, and as expected, observed no reaction. The reaction of chiral (R)-2-octanol with t-butyl dimethylsilyl chloride afforded **69** in good yield (Scheme 5-23). Treatment of **69** with lithium perchlorate afforded a 4.5:1 mixture of starting silyl ether and 2-octanol. The 2-octanol product was separated and optical rotation measurements showed no optical activity. This observation further confirmed the formation of

a carbocationic intermediate. In order to further confirm the formation of a ion pair, the deprotection of the recovered silyl ether starting material was carried out using tetrabutyl ammonium fluoride, and the optical activity of the 2-octanol formed was measured, revealing approximately 50% racemization during the perchlorate reaction. This observation is consistent with the formation of an ion pair and reattack of the $TBSO^-$ anion competing with attack from adventitious water.

Scheme 5-22



69

Conclusion

The study presented in this chapter makes an important contribution to a relatively new area of organic synthesis. In an effort to develop mild alternatives for commonly used organic reactions, we have found that lithium perchlorate in ether to be a unique environment for many transformations. In addition the previous reports showing the applicability of lithium perchlorate in Diels-Alder reactions, [2+2] cycloadditions, nucleophilic substitutions or even [1,3] sigmatropic rearrangements, our study has found that this

medium can effect eliminations of allylic esters, dehydration of secondary allylic alcohols, and hydrolysis of silyl enol ethers of allylic and benzylic alcohols. The study also helps gain more insight into the carbocationic nature of the intermediates involved.

CHAPTER 6
EXPERIMENTAL

General Methods

Infrared spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer and are reported in wave numbers (cm^{-1}). ^{1}H Nuclear magnetic resonance spectra were recorded on a Varian VXR-300 (300 MHz) and General Electric QE-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the above mentioned spectrophotometers. Chemical shifts are reported in ppm down field relative to tetramthylsilane as an internal standard. All reactions were run under an inert atmosphere of argon using oven dried apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography, Gas Chromatography, and NMR spectroscopy. Solvents and reagents were dried according to established procedures by distillation under inert atmospheres from appropriate drying agents. Analytical TLC was performed using Whatman 4410-222 precoated silica gel plates (0.25 mm) using UV light or phosphomolybdic acid in ethanol as an indicator. Column chromatography was performed using Kieselgel silica gel 60 (230-400 mesh) by standard flash chromatographic techniques.[80] Microscale purifications were performed using preparative TLC on Whatman 4851-840

precoated silica gel plates (1 mm) using UV light as an indicator.

Experimental Procedures and Results

4-(2,6,6-Trimethyl-2,3-epoxycyclohexan-1-yl)-3-buten-2-one (6).[82] To a solution of α-ionone (5.0 g, 26 mmol) in 30 mL of methylene chloride at -78°C was added a solution of MCPBA (7.8 g, 26 mmol) in 120 mL methylene chloride, via an addition funnel. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then washed with three 200 mL portions of 10% NaOH, followed by two portions of 200 mL water. The organic layer was dried and evaporation of the methylene chloride yielded 5.3 g of crude epoxide **6**. Gas chromatography showed that the mixture contained 91 % **6** and 9% of a byproduct. The crude mixture was purified by flash chromatography (85% hexane-ethyl acetate) and 4.1 g (77%) of pure epoxide were obtained as an oil: IR (neat oil) 2959 (s), 1755 (s), 1669 (m), 1446 (m), 1372 (s), 1223 (s), 1093 (s), 941 (m) cm^{-1}; 300 MHz ^{1}H NMR δ 0.76 (3H, s), 0.93 (3H, s), 1.05 (1H, m), 1.26 (3H, s), 1.45 (1H, m), 1.95 (2H, m), 2.10 (1H, d, J = 10 Hz), 2.30 (3H, s), 3.11 (1H, t, J = 2 Hz), 6.10 (1H, d, J = 16 Hz), 6.70 (dd, 1H, J = 10 Hz, J = 16 Hz); ^{13}C NMR (75 MHz) δ 20.46, 26.76, 27.79, 30.58, 32.57, 35.23, 35.57,

55.47, 82.48, 118.28, 151.02, 173.63, 204.44; m/z 209, 181, 163, 153, 135, 125, 109, 95.

(2,6,6-Trimethyl-2,3-epoxycyclohexan-1-yl) methanal (7).[83] A solution of **6** (7 g, 33 mmol) dissolved in CH_2Cl_2 (100 mL) was cooled to -78°C, and ozone (generated by a Welsbach model T-23 ozonizer operating at 8 psi with a flow rate of 0.015 ft^3/min) was bubbled through the solution. After two hours, the solution turned from blue to yellow. The ozone was then replaced by nitrogen, and dimethylsulfide (21 mL, 360 mmol) was added. The reaction was allowed to warm to room temperature overnight. Brine was added, the layers were separated, the organic layer was washed with brine while the aqueous layer was extracted with methylene chloride. The combined organic layers were then dried, the methylene chloride was evaporated, yielding **7** (4.6 g, 27 mmol) as a yellow oil. Flash chromatography yielded pure **7** (3.9 g, 23 mmol) as a clear liquid. IR (neat) 2958, 1719, 1452, 1032 cm^{-1}; 300 MHz ^{1}HNMR δ 0.83 (6H, s), 1.0-1.9 (5H, m), 1.24 (3H, s), 3.0 (1H, s), 9.6 (1H, d, J = 2 Hz); ^{13}C NMR (75 MHz) δ 203.7, 59.1, 57.5, 57.1, 30.0, 28.8, 27.6, 26.4, 24.3, 21.3. HRMS calcd for $C_{10}H_{16}O_2$ (M-1): 167.1072 , found 167.1062.

(2,6,6-Trimethyl-3-hydroxycyclohexen-1-yl)-methanal (8).[84] Aldehyde **7** (3.5 g, 21 mmol) was dissolved

in 30 mL methanol and 2.5 g potassium carbonate were added. The resulting suspension was stirred for three hours at room temperature, the potassium carbonate was then removed by filtration and the methanol was evaporated. The residue was dissolved in water and neutralized with 10 % HCl, followed by multiple extractions with ether. The organic layer was washed with three 50 mL portions of water, dried over anhydrous magnesium sulfate and the ether was then evaporated yielding **8** (3.3 g, 20 mmol) as an oil. Further purification was not possible due to the high decomposition rate of this system. 300 MHz ^{1}H NMR δ 1.15 (3H, s), 1.23 (3H, s), 1.35-2.0 (4H, m), 2.2 (3H, s), 4.05 (1H, t, J = 6 Hz), 10.1 (1H, s); ^{13}C NMR (75 MHz) δ 194.1, 153.4, 141.5, 71.2, 36.2, 33.8, 28.2, 27.8, 27.6, 15.8. HRMS calcd for $C_{10}H_{16}O_2$: 168.1072 , found 168.1150.

[2,6,6-trimethyl-3-hydroxycyclohexen-1-yl]ethene (9). To a solution of methyltriphenylphosphonium bromide (4.2 g, 12 mmol) dissolved in THF (100 mL) was added a 1.5M solution of nBuLi in hexanes (8.0 mL, 12 mmol). A solution of **8** (800 mg, 4.8 mmol) dissolved in THF (8 mL) was added slowly. The reaction was stirred at room temperature for 12 hours, diluted with diethyl ether (100 mL), and stored in the freezer overnight. The precipitated triphenylphosphine oxide was removed by filtration through a bed of celite. The organic phase was washed with brine, dried and the ether was

removed under reduced pressure, yielding **9** (700 mg, 4.2 mmol) as a dark oil. Purification using flash chromatography yielded **9** (600 mg, 3.6 mmol) as a clear liquid. 300 MHz ^{1}H NMR δ 1.0 (3H, s), 1.05 (3H, s), 1.35-1.45 (1H, m), 1.60-2.00 (3H, m), 1.80 (3H, s), 4.0 (1H, t, J = 5 Hz), 5.0 (1H, dd, J = 2 Hz, J = 18 Hz), 5.30 (1H, dd, J = 2 Hz, J = 11 Hz), 6.2 (1H, dd, J = 11 Hz, J = 17 Hz). ^{13}C NMR (75 MHz) δ 142.3, 134.8, 129.2, 118.9, 70.0, 34.2, 34.1, 28.6, 27.0, 18.1.

1-[2,4,4-trimethyl-3-(vinyl)cyclohexen-2-yl]-1-trimethylsilyl propynoate (10). To a solution of **9** (500 mg, 3 mmol) in methylene chloride (50 mL) was added trimethylsilylpropynoic acid (420 mg, 3 mmol) , followed by a solution of dicyclohexylcarbodiimide (620 mg, 3 mmol) in methylene chloride (25 mL), and 50 mg dimethylaminopyridine. The solution was stirred at room temperature for 10 hours, diluted with diethyl ether, filtered over a bed of celite, washed with cold 5% hydrochloric acid solution, saturated sodium bicarbonate and then brine. The organic layer was then dried and the solvent removed under vacuo, yielding **10** as an oil. Further purification using flash chromatography yielded **10** as a low melting solid (700 mg, 2.3 mmol). 300 MHz ^{1}H NMR δ 0.2 (3H, s), 1,05 (3H, s), 1.3-1.4 (1H, m), 1.6-1.9 (3H, m), 1.7 (3H, s), 5.05 (1H, dd, J = 2 Hz), 5.2-5.4 (2H, m), 6.2 (1H, dd, J = 11 Hz, J = 17 Hz); ^{13}C NMR (75 MHz) δ

153.6, 145.2, 135.1, 123.6, 119.3, 85.1, 74.0, 72.6, 34.2, 33.9, 28.4, 24.8, 17.9, 3.7, 0.9.

4-[2,6,6-trimethyl-3-hydroxycyclohexen-1-yl]-3-buten-2-one (11). Epoxyionone **6** (2.06 g, 9.91 mmol) was dissolved in 30 mL methanol and 1.5 g potassium carbonate were added. The resulting suspension was stirred for three hours at room temperature, then refluxed overnight. The potassium carbonate was then removed by filtration and the methanol was evaporated. The residue was dissolved in water and neutralized with 10 % HCl, followed by multiple extractions with ether. The organic layer was washed with three 50 mL portions of water, dried over anhydrous magnesium sulfate and the ether was then evaporated. 1.52 g (74%) of **11** was isolated as an oil: 300 MHz ^{1}H NMR δ 1.05 (6H, d, J = 7 Hz), 1.4 (1H, m), 1.7 (1H, m), 1.8 (1H, m), 1.85 (3H, s), 1.9 (1H, m), 2.3 (3H, s), 2.5 (1H, m), 4.05 (1H, t, J = 3 Hz), 6.15 (1H, d, J = 14 Hz), 7.2 (1H, d, J = 14 Hz); ^{13}C NMR (75 MHz) δ 198.8, 143.1, 141.4, 134.6, 132.9, 69.7, 34.8, 34.6, 28.8, 28.3, 27.6, 27.3, 18.5; MS m/z 208 (M^{+}), 175, 123, 109, 83 (base); HRMS calcd for $C_{13}H_{20}O_2$: 208.1463 found: 208.1450.

1-[2,4,4-trimethyl-3-(2-oxo-3-buten-4-yl) cyclohexen-2-yl] butynoate (4). 1.41 g (6.8 mmol) of **11**

were dissolved in 15 mL methylene chloride at 0°C. 2-Butynoic acid (0.62 g, 7.3 mmol) and DMAP (93 mg) were added. After 5 minutes, a solution of 1.56 g DCC in 15 mL methylene chloride was added slowly. A cloudy precipitate was observed. The reaction was stirred for 6 hours at room temperature, diluted with methylene chloride and the precipitate was removed by filtration. The filtrate was dried and upon the evaporation of the solvent, 1.7 g **4** were isolated. Purification by flash chromatography yielded 1.22 g (66%) pure **4** as an oil: IR (neat oil) 2936, 2240, 1704, 1672, 1253, 1065 cm^{-1}; 300 MHz ^1H NMR δ 1.05 (6H, d, J = 7 Hz), 1.4 (1H, m), 1.65 (1H, m), 1.7 (3H, s), 1.8 (1H, m), 1.9 (1H, m), 2.0 (3H, s), 2.3 (3H, s), 2.3 (3H, s), 5.3 (1H, s), 6.1 (1H, d, J = 14 Hz), 7.15 (1H, d, J = 14 Hz). ^{13}C NMR (75 MHz) δ 198.0, 153.5, 142.4, 141.8, 133.5, 128.7, 85.8, 73.5, 72.5, 34.5, 34.4, 28.6, 27.5, 27.1, 24.9, 18.3, 3.8.

1-[2,4,4-trimethyl-3-(2-oxo-3-buten-4-yl) cyclohexen-2-yl] fumarate (12). The diene **11** (160 mg, 1.0 mmol) was dissolved in 6 mL methylene chloride and cooled to 0°C. Fumaric acid monoethyl ester (500 mg, 1.5 mmol), along with 8 mg (.04 mmol) DMAP were added. After 5 minutes, 310 mg (1.5 mmol) of DCC in 3 mL methylene chloride were added. The reaction mixture was stirred overnight. 180 mg of crude **12** were isolated. Purification using preparative TLC was done and yielded 150 mg (59%) of pure **12** as an oil.

300 MHz ^{1}H NMR δ 1.05 (3H, s), 1.10 (3H, s), 1.30 (3H, t, J = 6 Hz), 1.40-2.05 (4H, m), 1.70 (3H, s), 2.30 (3H, s), 4.25 (2H, q, J = 6 Hz), 5.35 (1H, t, J = Hz), 6.15 (1H, d, J = 16 Hz), 6.90 (2H, s), 7.20 (1H, d, J = 16 Hz); ^{13}C NMR (75 MHz) δ 198.1, 164.9, 164.8, 142.3, 141.9, 133.8, 133.7, 133.5, 129.0, 73.0, 61.3, 34.6, 34.5, 28.7, 27.5, 27.1, 25.0, 18.3, 14.1. HRMS calcd for $C_{19}H_{22}O_5$: 320.1623, found 320.1484.

Ethyl 2-chloro-3-phenylsulfonyl propenoate (14).[85] Ethyl acrylate (7.5 g, 74 mmol) was added to a solution of benzenesulfenyl chloride (10.54 g, 73 mmol) in methylene chloride at 0°C. The reaction was stirred overnight and the product was isolated by evaporating the solvent. The reaction yielded 15.7 g (68 mmol) of **13**. The crude material was used in the preparation of **14** by adding g 60 g of MCPBA (50%) to a solution of **13** in methylene chloride at 0°C. The mixture was stirred for one hour, followed by the addition of 100 mL methylene chloride. The mixture was washed with five 100 mL portions of sodium bicarbonate and two 100 mL portions of brine. The organic layer was dried and the solvent was evaporated yielding 16.5 (60 mmol) of **14** as on oil: 300 MHz ^{1}H NMR δ 1.3(3H, t, J = 7 Hz), 3.65 (1H, dd, J = 10 Hz, 3 Hz), 4.05 (1H, dd, J = 10 Hz, 7 Hz), 4.6 (1H, dd, J = 7 Hz, 3 Hz), 7.6 (2H, d, J = 7 Hz), 7.7 (1H, t, J = 7 Hz), 7.95 (2H, d, J = 7 Hz).

Ethyl 3-phenylsulfonyl propenoate (15).[85] To a solution of **14** in methylene chloride at -78°C were added a few drops of DBN. After a few minutes, the formation of a thick oil was observed. The temperature was then raised to -5°C and the addition of DBN (7.44 g, 60 mmol) was completed slowly. The reaction was stirred overnight, then diluted with methylene chloride. The organic layer was washed with 2 % HCl, water and then brine. The solvent was dried and evaporated. Purification of the crude product yielded 10.05 g (42 mmol) of pure **15** as a yellow solid: 300 MHz ^{1}H NMR δ 1.32 (3H, t, J = 7 Hz), 4.25 (2H, q, J = 7 Hz), 6.85 (1H, d, J =15 Hz), 7.35 (1H, d, J = 15 Hz), 7.6 (1H, m), 7.9 (2H, d, J = 7 Hz), 8.05 (2H, d, J = 7 Hz); ^{13}C NMR (75 MHz) δ 170.6, 133.81, 130.19, 129.80, 129.58, 128.28, 128.26, 62.03, 13.97. 13.97.

3-phenylsulfonyl propenoic acid (16).[85] Ester **15** was added to a 100 mL 4 N HCl solution. The mixture was heated in a 110 °C bath for 85 hours. The oil gradually disappeared, and on cooling white crystals precipitated. The mixture was extracted with ether and the ether layer was washed with 10 % NaOH several times. The aqueous layer was then acidified and extracted with ether. The ether layer was dried and evaporated. Multiple recrystallizations of the residue yielded 1.27 g (48%) of pure **16** as white crystals,

m.p. 102-103°C: 300 MHz ^{1}H NMR δ 6.1 (1H, d, J = 14 Hz), 6.9 (1H, d, J = 14 Hz), 7.4 (1H, d, J = 14 Hz), 7.6 (2H, t, J = 7 Hz), 7.7 (1H, t, J = 7 Hz), 7.9 (2H, d, J = 7 Hz).

1-[2,4,4-trimethyl-3-(2-oxo-3-buten-4-yl) cyclohexen-2-yl] 3-phenylsulfonylpropenoate (17). The diene **11** (90 mg, .43 mmol) was dissolved in 6 mL methylene chloride and cooled to 0°C. The carboxylic acid **16** (100 mg, 0.47 mmol), along with 8 mg (.04 mmol) DMAP were added. After 5 minutes, 98 mg (.47 mmol) of DCC in 3 mL methylene chloride were added. The reaction mixture was stirred overnight. 160 mg of crude **17** were isolated. Purification using preparative TLC was carried out and yielded 132 mg of pure **17** as a white solid; 300 MHz ^{1}H NMR δ 1.05 (6H, d, J = 7 Hz), 1.45 (2H, m), 1.7 (3H, s), 1.75 (1H, m), 1.95 (1H, m), 2.3 (3H, s), 5.3 (1H, t, J = 2 Hz), 6.2 (1H, d, J = 16 Hz), 6.8 (1H, d, J = 16 Hz), 7.2 (1H, d, J = 16 Hz), 7.3 (2H, t, J = 7 Hz), 7.6 (2H, t, J = 7 Hz), 7.9 (2H, d, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 198.1, 163.3, 143.3, 142.8, 141.7, 138.3, 134.4, 133.6, 131.1, 129.6, 128.4, 74.0, 34.5, 34.4, 28.7, 27.5, 27.0, 24.9, 18.4. HRMS calcd for $C_{22}H_{26}SO_5$: 402.1500 found: 402.1486.

(2aβ,8aβ,8bβ)-3,6,6,8b-tetramethyl-4-acetyl-2a,7,8,8a-hexahydro-2H-naphto-[1,8-bc]furan-2-one

(20). Acetylynic ester **4** (2 g, 7.7 mmol) was dissolved in 10 mL xylenes and a few crystals of BHT were added. The mixture was deoxygenated very carefully and the tube was sealed using a hydrogen-oxygen flame. The reaction was heated at 180°C for 26 hours and yielded 1.93 g of crude material. Purification by flash chromatography yielded 1.7 g of **20** as an oil. Further purification by repeated recrystallizations from hexane/methylene chloride yielded 1.3 g of white crystals which were used for X-Ray diffraction studies. m.p. 120-122°C; IR (KBr) 1760, 1684, 1630, 1591, 1370, 1280 cm^{-1}. 300 MHz 300 MHz ^{1}H NMR δ 1.18 (6H, d, J = 2 Hz), 1.24 (3H, s), 1.35 (1H, m), 1.38 (1H, m), 1.6 (2H, m), 2.1 (1H, m), 2.2 (3H, s), 4.4 (1H, m), 6.25 (1H, s), 7.25 (1H, s); 75 MHz ^{13}C NMR δ 21.23, 21.66, 22.02, 27.89, 30.03, 30.37, 32.94, 34.71, 42.67, 58.75, 8.75, 118.63, 133.00, 134.33, 143.4, 174.9; IR 1760, 1684, 1630, 1591, 1370, 1280 cm^{-1}. MS m/z 274 (M^{+}), 229, 215; HRMS calcd for $C_{17}H_{22}O_3$: 274.1568 found: 274.1559. Anal calcd for $C_{17}H_{22}O_3$: C, 74.41; H, 8.08 found: C, 73.77, H, 8.14.

X-ray experimental for 20: Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_{α} radiation (l = 0.71073 Å). Cell parameters were refined using 1960 reflections. A hemisphere of data (1982 frames) was collected using the ω-scan method (0.3∞ frame width). The first 50 frames were re measured at the end of data collection to monitor instrument and crystal stability

(maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5,*[86] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. 255 parameters were refined in the final cycle of refinement using 1517 reflections with $I > 2\sigma(I)$ to yield R_1 5.16% and ωR_2 of 5.3% , respectively. Refinement was done using F^2.

(2aβ,8aβ,8bβ)-3,6,6,8b-Tetramethyl-4-acetyl-2a,7,8,8a-hexahydro-2H-naphto-[1,8-bc]furan-2-one (21). Phenylsulphonylpropenoate **17** (1 g, 2.48 mmol) was dissolved in 10 mL xylenes and a few crystals of BHT were added. The mixture was deoxygenated very carefully and the tube was sealed using a hydrogen-oxygen flame. The reaction was heated at 190°C for 30 hours and yielded 0.84 g of crude material. Purification by flash chromatography yielded 0.48 g of **21** as an oil. Further purification by repeated recrystallizations from hexane/methylene chloride yielded 0.30 g of white crystals, m.p. = 125-126°C; IR (cm^{-1}) 2947, 1754, 1678, 1355, 1168, 1014; 300 MHz ^1H NMR δ 1.21 (3H, s), 1.45 (3H, s), 1.61 (1H, m), 1.91 (2H, m), 2.41 (1H, m), 2.61 (3H, s), 2.77(3H, s), 5.15 (1H, dd, *J* = Hz, *J* =), 7.64 (1H, s); ^{13}C NMR (75

MHz) δ 14.3, 26.2, 30.5, 30.9, 31.74, 34.4, 37.1, 77.1, 123.4, 130.1, 136.6, 139.9, 141.8, 150.2, 170.1, 201.6.

3,4-dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-acid chloride (27). The commercially available 3,4 dihydro-2,2-dimethyl-4-oxo-2*H*-pyran-6-carboxylic acid (1.5 g, 8.9 mmol) was suspended in 25 mL methanol and lithium carbonate (1.1 equiv.) was added with vigorous stirring for 30 minutes. The methanol was then removed under reduced pressure and replaced with THF, which was evaporated and this process repeated three times. The resulting THF solution was cooled to 0°C under inert atmosphere. A THF solution containing oxallyl chloride (1.35 g, 8.9 mmol) was added slowly. The mixture was stirred overnight. The solid lithium bicarbonate and lithium chloride were removed by transferring the solution into a different flask via a cannula, under inert conditions. Evaporation of the solvent yielded 1.5 g of pure acid chloride **27**: 300 MHz ^{1}H NMR ($CDCl_3$) d 1.5 (6H, s), 2.55 (2H, s), 6.27 (1H, s).

Butyl 2,2-dimethyl-4-hydroxy-3,4-dihydro-2*H*-pyran-6-carboxylate (28). To a stirred solution of butopyronoxyl (10 g, 44 mmol) in THF (50 mL) at -78°C was added a 1.0 M solution of DIBAL-H in hexanes (53 mL) over a period of one hour. The solution was stirred at -78°C for 4

hours, then allowed to slowly warm to room temperature and stirred overnight. After cooling again to -78°C, the reaction was quenched with methanol (10 mL) and the resulting mixture poured into 100 mL of a saturated sodium potassium tartrate solution (Rochelle's Salt), and stirred for four hours. The layers were separated, the aqueous layer extracted with methylene chloride and the organic combined organic layers washed with brine. After drying the solvent was evaporated under reduced pressure to yield 9.47 g of crude alcohol **28**. Further purification by flash chromatography yielded 9.02 g (90%) of pure **28** as a colorless oil: 300 MHz ^{1}H NMR δ.95 (3H, J = 7 Hz), 1.25 (3H, s), 1.38 (2H, sextet, J = 7 Hz), 1.45 (3H, s), 1.7 (2H, q, J = 7 Hz), 1.75 (2H, quintet, J = 6 Hz), 2.0 (2H, quintet, J = 6 Hz), 2.7 (1H, br s), 4.2 (2H, t, J = 7 Hz), 4.4 (2H, m), 6.0 (1H, d, J = 2 Hz); ^{13}C NMR (75 MHz) δ 13.1, 18.6, 25.5, 28.0, 30.5, 42.0, 62.0, 63.7, 110.5, 142.1, 163.2; IR 3444, 2960, 2074, 1724, 1642, 1273, 1211, 1096; HRMS m/z 228.13, 211.13, 125.07, 117.01, 98.03, 70.99, 57.08, 41.03. Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H: 8.83. Found: C, 62.85; H, 8.62.

Butyl 2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-carboxylate (29). Alcohol **28** (9.0 g; 39 mmol) was mixed with diisopropylethyl amine (5.6 g, 42.9 mmol) in DMF (14 mL). After 20 minutes, TBSCl (5.87 g, 39 mmol) dissolved in DMF (5 mL) was added slowly. The reaction

was allowed to stir overnight and then quenched by addition of water (5 mL), followed by the addition of ether (10 mL) and then 5% $NaHCO_3$ (10 mL). The mixture was extracted with ether, the ether layer washed with brine several times to remove the amine, and dried. Evaporation of the solvent afforded 12.69 g of **29**. Flash chromatography yielded 12.0 g (90 %) of pure product as an oil: 300 MHz ^1H NMR δ 0.1 (6H, d, J = 7 Hz), 0.95 (9H, s), 0.98 (3H, t, J = 7 Hz), 1.25 (3H, t, J = 7 Hz), 1.38 (2H, m), 1.45 (3H, t, J = 7 Hz), 1.7 (2H, q, J = 6 Hz), 1.75 (2H, q, J = 6 Hz), 4.2 (2H, t, J = 7 Hz), 4.4 (1H, m), 5.9 (1H, d, J = 2 Hz); ^{13}C NMR (75 MHz) δ -4.7, -4.5, 14.2, 16.8, 17.2, 19.6, 26.1, 27.0, 30.1, 42.5, 61.7, 65.0, 112.6, 142.6, 163.7; IR 2950, 2863, 1737, 1646, 1275, 1255, 1212, 1101; HRMS m/z 342.22, 327.21, 285.17, 229.07, 171.01, 167.03, 109.06, 73.02. Anal. Calcd. for $C_{18}H_{34}SiO_4$: C, 63.11; H: 10.06. Found: C, 62.76; H, 10.43.

[2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-yl]methanol (30). To a solution of **29** (2g, 5.9 mmol) dissolved in THF (20 mL) at -78°C was added a 1.0 M DIBAL-H solution (13.5 mL, 13.5 mmol). The reaction was stirred at -78°C for four hours and then allowed to warm to room temperature overnight. The workup was identical to that of compound **28**. The reaction yielded 1.60 g (98%) of pure **30** with no further purification required: 300 MHz ^1H NMR ($CDCl_3$) d 0.1 (6H, d, J = 7 Hz), 0.9 (9H, s), 1.25 (3H, s),

1.35 (3H, s), 1.6 (1H, dd), 1.7 (1H, dd), 2.3 (1H, br s), 3.9 (2H, br s), 4.3 (1H, m), 4.7 (1H, d, J = 2 Hz); ^{13}C NMR (75 MHz) δ -4.7, -4.5, 18.1, 24.5, 24.7, 28.1, 42.3, 62.2, 62.4, 75.8, 100.1, 152.1; IR 3373, 2940, 2860, 1675, 1468, 1368, 1257, 1076; HRMS m/z 273.18, 255.19, 217.13, 199.15, 157.06, 141.09, 115.09, 109.07. Anal. Calcd. for $C_{14}H_{28}SiO_3$: C, 61.71; H: 10.36. Found: C, 61.94; H, 10.62.

[2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-yl]methanal (31). To oxallyl chloride (0.235 mL, 2.75 mol) in methylene chloride (5 mL) was added DMSO (0.39 mL, 5.5 mmol) at -78°C over a period of 5 minutes. The mixture was stirred at -78°C for 10 minutes. A methylene chloride solution of **30** (700 mg, 2.5 mmol) was then added slowly and the mixture was stirred for two hours at -78°C, followed by the addition of triethylamine (1.7 mL, 12.5 mmol). The reaction was stirred for two hours, water added and the mixture was extracted with methylene chloride. The organic layer was separated and washed with brine, dried and evaporated, affording 580 mg of crude **31**. Further purification by flash chromatography on alumina with hexane yielded 510 mg of pure aldehyde **31** (73 %) as an oil: 300 MHz ^1H NMR ($CDCl_3$) δ 01. (6H, d, J = 7 Hz), 0.9 (9H, s), 1.27 (3H, s), 1.4 (3 H, s), 1.7 (1H, dd), 1.85 (1H, dd), 4.5 (1H, m), 5.7 (1H, d, J = 2 Hz), 9.2 (1H, s); ^{13}C NMR (75 MHz) δ -4.67, -4.58, 18.09, 25.78, 26.07, 27.40, 42.34, 62.23,

76.73, 121.52, 150.76, 187.80; HRMS m/z 270.16, 231.98, 213.09, 199.08, 158.03, 157.03, 113.04, 93.07. Anal. Calcd. for $C_{14}H_{26}SiO_3$: C, 62.18; H: 9.69. Found: C, 61.93; H, 9.61.

[2,2-dimethyl-4-(hydroxy)-3,4-dihydro-2*H*-pyran-6-yl]methanol (32). To a solution of butopyronoxyl (20 g, 88 mmol) in THF (500 mL) cooled to -78°C was added a 1.0 M DIBAL solution in hexanes (300 mL, 300 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with methanol (10 mL) and poured onto 1000 mL of saturated sodium potassium tartrate solution, followed by vigorous stirring for 5 hours. The layers were separated and the organic layer was washed with small portions of brine, dried over magnesium sulfate and anhydrous potassium carbonate. Removal of the solvent under reduced pressure yielded **32** (16 g) as a yellow oil. Further purification using flash chromatography was attempted but was unsuccessful due to the high instability of the diol. 300 MHz ^{1}H NMR δ 1.25 (3H, s), 1.35 (3H, s), 1.8 (2H, dd, J = 7 Hz, J = 100 Hz), 3.95 (2H, brs), 4.35 (1H, m), 4.9 (1H, d, J = 2 Hz); ^{13}C NMR (75 MHz) δ 146.5, 98.6, 76.0, 63.5, 62.1, 43.5, 25.1, 28.2.

[2,2-dimethyl-3,4-dihydro-2*H*-pyran-6-yl]methanal (33). A sample of crude diol **32** (10 g, 63 mmol) was placed

into a simple distillation apparatus and heated to 180°C for two hours. The evolution of a gas was observed (later explained as the loss of water). The product **33** was collected as a clear liquid with a boiling point between 60-70°C at 1 atm. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3 (6H, s), 1.7 (2H, m), 2.3 (2H, m), 5.9 (1H. m), 9.1 (1H, d); ^{13}C NMR (75 MHz) δ 187.2, 152.0, 122.1, 75.0, 32.5, 26.5, 19.8.

[2,2-dimethyl-4-hydroxy-3,4-dihydro-2*H*-pyran-6-yl]methanal (34). To oxallyl chloride (0.47 mL, 5.5 mmol) in methylene chloride (5 mL) was added DMSO (0.8 mL, 11 mmol) at -78°C over a period of 5 minutes. The mixture was stirred at -78°C for 10 minutes. A methylene chloride solution of **32** (800 mg, 5 mmol) was then added slowly and the mixture was stirred for two hours at -78°C, followed by the addition of triethylamine (3.5 mL, 25 mmol). The reaction was stirred for two hours, water added and the mixture was extracted with methylene chloride. The organic layer was separated and washed with brine , dried and evaporated, affording 680 mg of crude **34**. Further purification by flash chromatography on alumina with hexane yielded 620 mg of pure aldehyde **34** as an oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, s), 1.5 (3H, s), 2.2 (2H, dd, J = 7 Hz, J = 60 Hz), 3.3 (1H, brs), 4.8 (1H, m), 5.8 (1H, d, J = 2 Hz), 9.2 (1H, s); ^{13}C NMR (75 MHz) δ 187.1, 150.9, 118.2, 48.6, 42.5, 27.5, 25.1.

Dispiroacetal dimer (35). To a solution of **30** (200 mg, 0.74 mmol), dissolved in diethyl ether (0.5 mL), was added triethylamine (75 mg, 0.75 mmol), and a 1.0 M diethyl ether solution of hydrochloric acid (0.75 mL, 0.75 mmol). The mixture was stirred for eight hours at room temperature, and then diluted with diethyl ether (25 mL). Water was added, and the layers were separated. The organic layer was washed with sodium bicarbonate, brine and water, separated and dried over magnesium sulfate. The ether was evaporated under vacuo, affording 190 mg of crude **35**. Careful purification by flash chromatography on silica gel afforded 180 mg of pure **35** as a white solid (m.p. = 142-150°C), which by NMR consisted of a 1:1 mixture of diastereomers of **35**.

Diastereomer 1: 300 MHz ^{1}H NMR δ 0.05 (6H, s), 0.9 (9H, s), 1.4 (3H, s), 1.6 (3H, s), 1.7 (4H, m), 3.4 (1H, d, J = 11.4 Hz), 3.6 (1H, d, J = 11.4 Hz), 4.2 (1H, m). ^{13}C NMR (75 MHz) δ 98.3, 74.3, 66.2, 62.9, 46.7, 43.5, 40.9, 32.6, 27.6, 25.0, 18.1, -4.5.

Diastereomer 2: 300 MHz ^{1}H NMR δ 0.045 (6H, s), 0.85 (9H, s), 1.6 (3H, s), 1.8 (3H, s), 2.0 (2H, m), 2.3 (2H, m), 3.3 (1H, d, J = 11.4 Hz), 3.8 (1H, d, J = 11.4 Hz), 4.2 (1H, m). ^{13}C NMR (75 MHz) δ 95.3, 74.5, 66.9, 62.4, 46.9, 43.5, 40.9, 32.7, 27.6, 25.0, 17.9, -4.5.

HRMS calcd 545.3615, found 545.3654. Anal. Calcd. for $C_{14}H_{26}SiO_3$: C, 61.72; H: 10.37. Found: C, 62.02; H, 10.70.

X-ray experimental for 35: A solid sample of a mixture of diastereomers of **35** was recrystallized in ether and one diastereomer was isolated in the form of thin plates and submitted for X-ray analysis. Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å). Cell parameters were refined using 4587 reflections. A hemisphere of data (1381 frames) was collected using the ω-scan method (0.3° frame width). The first 50 frames were re measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5,*[86] and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. 255 parameters were refined in the final cycle of refinement using 2702 reflections with I > 2σ(I) to yield R_1 4.87% and ωR_2 of 10.22%, respectively. Refinement was done using F^2.

2,2-dimethyl-6-vinyl-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran (38). To a solution of methyl triphenylphosphonium iodide (1.49 g, 3.7 mmol) in THF (25 mL) cooled to -78°C was added a 2.5 M solution of nBuLi in hexanes (1.6 mL, 4 mmol). The reaction mixture turned deep

red. A solution containing **31** (1.0 g, 3.7 mmol) dissolved in THF (3 mL) was added slowly. The reaction mixture was allowed to warm to room temperature overnight, diluted with pentane and stored in the freezer. Filtration over celite removed the majority of the resulting phosphine oxide. The solution was then washed with brine, the organic layer was dried and the solvent evaporated under vacuo. The crude diene was then purified via flash chromatography using neutral alumina or deactivated silica gel, yielding 720 mg of **38** as an oil. 300 MHz ^{1}H NMR δ 0.1 (6H, d, J = 5 Hz), 0.9 (9H, s), 1.25 (3H, s), 1.4 (3H, s), 1.7 (1H, dd), 1.85 (1H, dd), 4.4 (1H, m), 4.8 (1H, d, J = 7 Hz), 5.05 (1H, dd, J = 2 Hz, J = 11 Hz), 5.55 (1H, dd, J = 2 Hz, J = 17 Hz), 6.05 (1H, dd, J = 11 Hz, J = 17 Hz); ^{13}C NMR (75 MHz) d 149.5, 133.0, 113.8, 104.5, 74.7, 62.8, 42.7, 27.3, 26.4, 24.8, 19.0, -4.5, -4.7. HRMS Calcd. for $C_{15}H_{28}SiO_2$ (M+1): 269.1930, found 269.1941.

2-(Diphenylphosphinoyl)-1,3-dioxane (39). Isopropyl diphenyl phosphinite was prepared by adding 900 mg of 60% sodium hydride dispersion to 5 mL dry isopropanol. After the evolution of hydrogen had ceased, chlorodiphenylphosphine (5.0 g, 22 mmol) was added slowly and the mixture was stirred for three hours. The isopropanol was removed under reduced pressure and replaced with toluene (20 mL). Commercially available N,N-dimethylformamide trimethylene acetal (3.0 g, 22 mmol) was converted into (1,3-

dioxan-2-yl) trimethylammonium iodide (6.25 g, 22 mmol) using freshly distilled methyl iodide (3.25 g, 22 mmol) in THF (10 mL), and then added to the toluene solution of isopropyldiphenylphosphinite. The reaction was refluxed for 6 hours, then cooled and concentrated to 10 mL. Petroleum ether was added, and the mixture was allowed to stand overnight in the freezer. The solid obtained was recrystallized from benzene-petroleum ether to afford **39** (4.5 g, 15.6 mmol) as a white powder (m.p. 176-178°C). 300 MHz ^{1}H NMR δ 1.4 (2H, d, J = 12 Hz), 3.8 (2H, t, J = 12 Hz), 4.2 (2H, dd, J = 2 Hz, J = 12 Hz), 5.4 (1H, d, J = 6 Hz), 7.5 (4H, m), 7.7 (4H, m), 7.9 (4H, dd, J = 7 Hz, J = 13 Hz); ^{13}C NMR (75 MHz) δ 132.2, 132.1, 130.4 (d, J = 140 Hz), 128.2, 101.2 (d, J = 100 Hz), 68.3 (d, J = 10 Hz), 25.9. HRMS for $C_{16}H_{18}PO_3$ (M+1) calcd. 289.0993, found 289.0993.

2,2-dimethyl-6-methoxyvinyl-4-(t-butyldimethyl siloxy)-3,4-dihydro-2*H*-pyran (40). To a solution of (methoxymethyl)triphenylphosphonium bromide (340 mg, 1 mmol) in THF (25 mL) containing diisopropylethyl amine (230 mg, 2 mmol), cooled to -78°C was added a 2.5 M solution of nBuLi in hexanes (0.400 mL, 1 mmol). The reaction mixture turned deep red. A solution containing **31** (270 mg, 1 mmol) dissolved in THF (3 mL) was added slowly. The reaction mixture was allowed to warm to room temperature overnight, diluted with pentane and stored in the freezer. Filtration over celite removed the

majority of the resulting phosphine oxide. The solution was then washed with brine, the organic layer was dried and the solvent evaporated under vacuo. The crude diene was then purified via flash chromatography using neutral alumina or deactivated silica gel, yielding 170 mg of **40** as an oil. 300 MHz ^{1}H NMR δ 0.1 (6H, s), 0.8 (9H, s), 1.15 (3H, s), 1.25 (3H, s), 1.65 (1H, dd), 1.85 (1H, dd), 3.6 (3H, s), 4.4 (1H, m), 4.6 (1H, d, *J* = 3 Hz), 5.2 (1H, d, *J* = 11 Hz), 6.8 (1H, d, *J* = 11 Hz). ^{13}C NMR (75 MHz) d 151.2, 133.4, 128.7, 127.2, 75.1, 63.2, 56.2, 43.3, 28.7, 26.9, 25.9, -4.9, -5.2.

2,2-dimethyl-6-(1,3-dithianylidene)-4-(t-butyl dimethylsiloxy)-3,4-dihydro-2*H*-pyran (42). To a solution of 2-trimethylsilyl-1,3-dithiane (190 mg, 1 mmol) dissolved in THF (3 mL) was added a 2.5 M solution of nBuLi in hexanes (.40 mL, 1 mmol). After 15 minutes, a solution of aldehyde **31** (270 mg, 1 mmol) was added. The reaction was stirred for 1 hour, quenched with brine (50 mL), and the product was extracted with methylene chloride. The organic layer was dried and evaporated, affording **42** (320 mg, 0.86 mmol) as an oil. Further purification was not necessary. 300 MHz ^{1}H NMR δ 0.05 (6H, d, J = 2 Hz), 0.9 (9H, s), 1.25 (3H, s), 1.4 (3H, s), 1.85 (2H. m), 2.1 (2H, m), 2.95 (4H, m), 4.4 (1H, m), 4.8 (1H, d, *J* = 3 Hz), 6.0 (1H, s); ^{13}C NMR (75 MHz) δ 149.0, 133.8, 121.9, 104.1, 75.24, 62.7, 42.3, 30.9, 29.0,

28.2, 25.8, 23.9, -3.2. HRMS calcd. (M+1): 373.1691 found: 373.1628.

Open 1,3 dithianylidine (43). To a solution of **42** (250 mg, 0.7 mmol) dissolved in benzene (2 mL) was added 3-ethyl phenyl propiolate (300 mg, 1.8 mmol), along with 10 mg of BHT. The solution was heated at 90°C overnight, the solvent removed under vacuo and the mixture was separated via flash chromatography to yield **40** (140 mg, 0.58 mmol) as a yellow low-melting waxy solid. 300 MHz ^{1}H NMR δ 1.95 (6H, d, J = 7 Hz), 2.22 (2H, quintet, J = 7 Hz), 3.0 (2H, t, J = 7 Hz), 3.05 (2H, t, J = 7 Hz), 6.0 (1H, d, J = 12 Hz), 6.1 (1H, d, J = 14 Hz), 6.75 (1H, s), 7.50 (1H, dd, J = 12 Hz, J = 14 Hz); ^{13}C NMR (75 MHz) δ 185.7, 161.3, 146.5, 138.1, 128.0, 124.5, 121.3, 28.8, 28.1, 26.7, 23.86, 19.0. HRMS for $C_{12}H_{16}OS_2$ calcd. 240.0720 , found 240.0621.

2,2-dimethyl-6-[2-(E)-carbethoxyvinyl]-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran (44). To a solution of hexamethyldisilazane (.8 mL, 2 mmol) in THF (20 mL) cooled at -78°C was added a 2.5 M solution of nBuLi (.5 mL, 2 mmol). The solution was allowed to warm to -40°C, and triethylphosphonoacetate (450 mg, 2 mmol) was added. After 15 minutes, a solution of aldehyde **31** (540 mg, 2 mmol) in THF (10 mL) was added. The mixture was allowed to slowly warm to

room temperature and stirred overnight. The reaction was transferred into a separatory funnel and 50 mL of water were added. The organic layer was separated, washed with brine, while the water layer was extracted with methylene chloride. The combined organic layers were dried and the solvent removed under reduced pressure, affording **44** (660 mg, 1.94 mmol)as a clear oil, without any further purification necessary. 300 MHz ^{1}H NMR δ 0.05 (6H, s), 1.0 (12H, brs), 1.4 (3H, s), 1.5 (3H, s), 2.0 (2H, dd, J = 6 Hz, J = 30 Hz), 4.4 (2H, q, J = 6 Hz), 5.3 (1H, d, J = 2 Hz), 6.4 (1H, d, J = 15 Hz), 7.1 (1H, J = 15 Hz); ^{13}C NMR (75 MHz) d 166.9, 148.2, 140.1, 118.3, 111.4, 62.5, 60.2, 42.2, 27.3, 26.3, 25.74, 18.0, 14.24, -4.6. HRMS calcd (M+1) 341.2148, found 341.2143.

2,2-dimethyl-6-[(E)-propene-3-ol]-4-(t-butyl dimethylsiloxy)-3,4-dihydro-2*H*-pyran (45). To a solution of ester **44** (680 mg, 2 mmol) in THF (50 mL) cooled to -78°C was added a 1.0 M DIBAL solution in hexanes (4.4 mL, 2.2 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with methanol (1 mL) and poured onto 100 mL of saturated sodium potassium tartrate solution, followed by vigorous stirring for 5 hours. The layers were separated and the organic layer was washed with small portions of brine, dried over magnesium sulfate and anhydrous potassium carbonate. Removal of the solvent under reduced pressure yielded **45** (580

mg, 1.9 mmol) as a yellow oil (85% yield). Further purification using flash chromatography was carried out, affording 500 mg of pure **45** as a white low-melting solid (m.p < 35°C). 300 MHz ^{1}H NMR δ 0.05 (6H, d, *J* = 2 Hz), 0.9 (9H, s), 1.2 (3H, s), 1.3 (3H, s), 1.8 (2H, m), 4.2 (2H, d, *J* = 7 Hz), 4.4 (1H, m), 4.8 (1H, d, *J* = 3 Hz), 5.9 (1H, d, *J* = 15 Hz), 6.1 (1H, dt, *J* = 5 Hz, *J* = 15 Hz) ^{13}C NMR (75 MHz) δ 146.8, 126.6, 124.1, 103.7, 74.2, 56.9, 42.6, 27.9, 26.4, 24.8, 18.1, -4.4, -4.6.

Deuterated Analog of 45 (45*d*$_2$). To a solution of ester **44** (340 mg, 1 mmol) in THF (25 mL) cooled to -78°C was added $LiAlD_4$ (42 mg, 1 mmol). The solution was stirred at -78°C for two hours. The reaction was quenched with methanol (1 mL) and poured onto 100 mL of saturated sodium potassium tartrate solution, followed by vigorous stirring for 5 hours. The layers were separated and the organic layer was washed with small portions of brine, dried over magnesium sulfate and anhydrous potassium carbonate. Removal of the solvent under reduced pressure yielded **45*d*$_2$** (300 mg, 0.9 mmol) as a yellow oil. Further purification using flash chromatography was carried out, affording 150 mg of pure **45** as a clear oil. 300 MHz ^{1}H NMR δ 0.05 (6H, d, *J* = 1 Hz), 0.9 (9H, s), 1.2 (3H, s), 1.3 (3H, s), 1.8 (2H, m), 4.4 (1H, m), 4.8 (1H, d, *J* = 3 Hz), 5.9 (1H, d, *J* = 15 Hz), 6.1 (1H, d, *J* = 15 Hz) ^{13}C NMR

(75 MHz) δ 148.8, 128.6, 126.1, 104.7, 74.2, 62.9, 42.6, 27.9, 26.4, 25.8, 18.1, -4.4, -4.6.

Substituted furan product(46). To a solution of **45** (260 mg, 0.88 mmol), dissolved in diethyl ether (0.5 mL), was added triethylamine (90 mg, 0.9 mmol), and a 1.0 M diethyl ether solution of hydrochloric acid (.9 mL, 0.9 mmol). The mixture was stirred for eight hours at room temperature, and then diluted with diethyl ether (25 mL). Water was added, and the layers were separated. The organic layer was washed with sodium bicarbonate, brine and water, separated and dried over magnesium sulfate. The ether was evaporated under vacuo, affording 230 mg of crude **46**. Careful purification by flash chromatography on silica gel afforded 115 mg of pure **46** (80% yield) as a yellow oil. 500 MHz ^{1}H NMR δ 1.29 (6H, s), 1.6 (1H, brs), 2.69 (2H, dd, J = 1.46 Hz, J = 7.82 Hz), 5.67 (1H, dt, J = 7.81 Hz, J = 11.72 Hz), 6.29 (1H, d, J = 3.41 Hz), 6.31 (1H, dt, J = 1.47 Hz, J = 11.8 Hz) 6.38 (1H, dd, J = 1.46 Hz, J = 3.41 Hz), 7.37 (1H, d, J = 1.46 Hz) ^{13}C NMR (75 MHz) δ 153.06, 141.41, 125.67, 119.45, 110.98, 109.51, 71.14, 42.90, 29.79. HRMS calcd 166.0993, found 166.0974.

Deuterated furan analog (46d_1). To a solution of **45**d_2 (130 mg, 0.44 mmol), dissolved in diethyl ether (0.5 mL), was added triethyl amine (45 mg, 0.5 mmol), and a 1.0 M

diethyl ether solution of hydrochloric acid (.5 mL, 0.55 mmol). The mixture was stirred for eight hours at room temperature, and then diluted with diethyl ether (25 mL). Water was added, and the layers were separated. The organic layer was washed with sodium bicarbonate, brine and water, separated and dried over magnesium sulfate. The ether was evaporated under vacuo, affording 120 mg of crude **46***d*$_1$. Careful purification by flash chromatography on silica gel afforded 65 mg of pure **46***d*$_1$ as a yellow oil. 500 MHz ^{1}H NMR δ 1.3 (6H, s), 1.6 (1H, brs), 2.7 (2H, dd, J = 1.46 Hz, J = 7.42 Hz), 5.67 (1H, dt, J = 7.81 Hz, J = 11.72 Hz), 6.29 (1H, d, J = 3.41 Hz), 6.31 (1H, d, J = 11.8 Hz) 6.38 (1H, d, J = 3.0 Hz); ^{13}C NMR (75 MHz) δ 154.6, 142.4, 126.6, 119.4, 110.9, 109.1, 71.4, 42.9, 29.7.

{(E)-{6[2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro]-2*H*-pyran}-2-propenyl}trimethylsilyl propynoate (47). The procedure used is the same as described above, using **45** (500 mg, 1.7 mmol), trimethylsilyl-propynoic acid (240 mg, 1.7 mmol), dicyclohexylcarbodiimide (390 mg, 1.9 mmol), and 10 mg of 4-dimethylaminopyridine (DMAP) as a catalyst. After purification via flash chromatography, 600 mg **47** were isolated. 300 MHz ^{1}H NMR δ 0.0 (9H, s), 0.05 (6H, d, J = 2 Hz), 0.9 (9H, s), 1.3 (3H, s), 1.35 (3H, s), 1.8 (2H, m), 4.4 (1H, m), 4.6 (2H, d, J = 3 Hz), 4.8 (1H, d, J = 3 Hz), 6.0 (1H, d, J = 15 Hz), 6.05 (1H,

dt, J = 5 Hz, J = 15 Hz) ^{13}C NMR (75 MHz) δ 155.3, 148.3, 129.6, 123.2, 105.5, 74.9, 64.4, 62,6, 42.6, 37.2, 27.3, 26.2, 25.7, 21.2, 18.4, 0.9, -4.5, -4.6.

{(E)-{6[2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro]-2*H*-pyran} 2-propenyl}2-butynoate (48). To a solution of **45** (2.4 g, 8 mmol) in methylene chloride (50 mL) was added trimethylsilylpropynoic acid (700 mg, 8 mmol), followed by a solution of dicyclohexylcarbodiimide (2.0 g, 9 mmol) in methylene chloride (50 mL), and 100 mg DMAP. The solution was stirred at room temperature for 10 hours, diluted with diethyl ether, filtered over a bed of celite, washed with cold 5% hydrochloric acid solution, saturated sodium bicarbonate and then brine. The organic layer was then dried and the solvent removed under vacuo, yielding **48** as an oil. Further purification using flash chromatography yielded **48** as a low melting solid (1.8 g, 4.8 mmol) (yield 58%). 300 MHz ^{1}H NMR δ 0.05 (6H, d, J = 2 Hz), 0.9 (9H, s), 1.3 (3H, s), 1.35 (3H, s), 1.8 (2H, dd, J = 6 Hz, J = 30 Hz), 2.0 (3H, s), 4.4 (1H, m), 4.6 (2H, d, J = 3 Hz), 4.8 (1H, d, J = 3 Hz), 6.0 (1H, d, J = 15 Hz), 6.05 (1H, dt, J = 5 Hz, J = 15 Hz) ^{13}C NMR (75 MHz) δ 153.1, 148.3, 130.2, 122.2, 105.6, 74.7, 65.3, 63.5, 55.5, 42.4, 34.7, 27.1, 26.5, 25.7, 24.5, -4.6, -4.8. HRMS calcd 364.2069, found 364.2054.

4-(t-Butyldimethylsiloxy)butynoic acid (49). A solution of t-butyldimethylsilyl chloride (18.0 g, 120 mmol) and DMAP (3 g, 24 mmol) in methylene chloride (30 mL) was cooled to 0°C. Triethylamine (13.2 g, 120 mmol) was added slowly, followed by the careful addition of a solution of propargyl alcohol (5.6 g, 100 mmol) in methylene chloride (15 mL). The reaction was exothermic and complete in 10 minutes, turning into a solid mass. Water was added, followed by sodium bicarbonate. The reaction was diluted with ether, the layers were separated, the organic layer was extracted with methylene chloride, while the aqueous layer was washed with brine. The combined organic layers were dried and the solvent was evaporated yielding t-butyldimethylsilyl propargyl ether as an oil, used directly in the next step. The yield was assumed to be quantitative. A 3.1 M solution of ethyl magnesium bromide in ether (39 mL, 125 mmol) was added to a to a THF solution of the previously prepared propargyl ether, and the resulting solution cooled to -30°C. The reaction mixture turned cloudy, and was stirred for 30 minutes at this temperature. Carbon dioxide (generated by heating dry ice in an Erlenmeyer flask and passing it through two drying tubes equipped with dry rite and calcium chloride, respectively) was bubbled through the solution for six hours, while keeping the temperature between -20°C and -10°C. The reaction mixture was poured onto ice and the layers were separated. The aqueous layer was acidified with concentrated HCl to pH = 1, while maintaining the temperature below 5°C,

in order to avoid cleavage of the silyl ether. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine to remove the propionic acid formed as a byproduct, dried, and evaporated, yielding **49** (13.6 g, 63 mmol) as a low-melting waxy white solid. 300 MHz ^{1}H NMR δ 0.05 (6H, s), 0.95 (9H, s), 4.42 (2H, s), 8.4 (1H, brs); ^{13}C NMR (75 MHz) δ 157.1, 88.5, 76.1, 51.4, 25.6, 18.2, -4.8, -5.2. HRMS calcd 214.1025, found 214.1031.

(E)-{6-[2,2-dimethyl-4-(t-butyldimethylsiloxy)]-3,4-dihydro-2*H*-pyran}-2-propenyl}(4-(t-butyldimethyl siloxy) -2-butynoate] (50). To a solution of **45** (1.2 g, 4 mmol) in methylene chloride (25 mL) was added butynoic acid **49** (860 mg, 4 mmol), followed by a solution of dicyclohexylcarbodiimide (1.0 g, 4.5 mmol) in methylene chloride (25 mL), and 50 mg DMAP. The solution was stirred at room temperature for 10 hours, diluted with diethyl ether, filtered over a bed of celite, washed with cold 5% hydrochloric acid solution, saturated sodium bicarbonate and then brine. The organic layer was then dried and the solvent removed under vacuo, yielding **50** as an oil. Further purification using flash chromatography yielded **50** as a clear oil (1.2 g, 2.4 mmol), 59% yield. 300 MHz ^{1}H NMR δ 0.05 (12H, m), 0.8 (9H, s), 0.9 (9H, s), 1.3 (3H, s), 1.35 (3H, s), 1.8 (2H, m), 4.4 (1H, m), 4.6 (2H, d, J = 3 Hz), 4.8 (1H, d, J = 3 Hz), 4.9 (2H, brs), 6.0 (1H, d, J = 15 Hz), 6.05 (1H, dt, J

= 5 Hz, J = 15 Hz) HRMS for $C_{26}H_{46}Si_2O_5$ (M+1) calcd 495.2883, found 495.2896.

2,2-dimethyl-6-[(E)-1-propynoxy-2-propenyl]-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran (51). To a solution of sodium hydride (480 mg, 20 mmol) in THF (25 mL) was added a solution of alcohol **45** (5.0 g, 17 mmol) in THF (15 mL). The mixture was stirred for 15 minutes, followed by the addition of propargyl bromide (3 g, 25 mmol). The reaction was stirred overnight at room temperature, and quenched with methanol (10 mL). Brine was added, the layers were separated, the organic layer was washed with brine, while the aqueous layer was washed with ethyl acetate. The combined organic layers were dried and the solvents removed, affording **51** (5.2 g, 15.5 mmol) as a brown oil. Further purification using flash chromatography afforded 4.8 g **51** as a dark yellow oil. 300 MHz ^{1}H NMR δ 0.05 (6H, d, J = 2 Hz), 0.9 (9H, s), 1.3 (3H, s), 1.35 (3H, s), 1.7 (2H, m), 2.4 (1H, brs), 4.2 (2H, d, J = 3 Hz), 4.25 (2H, d, J = 3 Hz), 4.4 (1H, m), 4.8 (1H, d, J = 3 Hz), 6.0 (1H, d, J = 15 Hz), 6.05 (1H, dt, J = 5 Hz, J = 15 Hz) ^{13}C NMR (75 MHz) δ 148.8, 128.9, 125.1, 104.7, 74.7, 74.3, 69.4, 62.7, 56.9, 42.6, 27.9, 26.4, 25.8, 18.0, -4.5, -4.7. HRMS calcd (M+1) calcd. 335.1964, found 335.2084

4-[2,6,6-trimethylcyclohex-1,3-dien-1-yl]-3-buten-2-one (52). To butynoate **4** (0.7 g, 3.4 mmol) was added a 5.0M solution of lithium perchlorate in diethyl ether (10.0 mL, 50 mmol). The mixture was stirred for 8 hours, turning from clear to bright green. Water was added, followed by ether, the layers were separated and the ether layer washed with saturated sodium bicarbonate, and then brine, dried and evaporated under reduced pressure, resulting in 0.6 g of **52** as an oil. Further purification via flash chromatography yielded **52** (0.5 g, 2.61 mmol) as a yellow liquid (77% yield). 300 MHz ^{1}H NMR δ 1.0 (6H, s), 1.84 (3H, s), 2.06 (2H, d, J = 2 Hz), 2.24 (3H, s), 5.80 (2H, s), 6.12 (1H, d, J = 16 Hz), 7.2 (1H, d, J = 16 Hz); ^{13}C NMR (75 MHz) δ 198.22, 141.67, 135.90, 132.69, 130.32, 129.58, 128.18, 39.95, 34.00, 27.31, 26.52, 20.28. HRMS for $C_{13}H_{19}O$ (M+1) calcd. 191.1435 , found 191.1455.

5,5-Dimethyl-3-vinylcyclohex-2-en-1-yl benzoate (54). To a solution of 5,5-dimethyl-3-vinyl-cyclohex-2-en-1-ol (1.52 g, 10 mmol) dissolved in diisopropylethylamine (10 mL) was added benzoyl chloride (2.8 g, 20 mmol). The reaction was stirred overnight with the gradual formation of a white precipitate. Ether was then added to the suspension, which was then washed with saturated sodium bicarbonate and brine, dried and the ether evaporated under reduced pressure, yielding 2.2 g of **54** as a mixture of product, unreacted

starting material and unreacted benzoyl chloride. Further purification via flash chromatography yielded 2.2 g (8.5 mmol) **54** as a clear oil. 300 MHz ^{1}H NMR δ 1.0 (3H, s), 1.05 (3H, s), 1.8 (2H, m), 2.0 (2H. d, J = 3 Hz), 5.05 (1H, d, J = 10 Hz), 5.25 (1H, d, J = 15 Hz), 5.7 (1H, brs), 5.8 (1H, brs), 6.4 (1H, dd, J = 10 Hz, J = 15 Hz), 7.4 (2H, t, J = 8 Hz), 7.6 (1H, t, J = 8 Hz), 8.0 (2H, d, J = 8 Hz); ^{13}C NMR (75 MHz) δ 166.12, 138.95, 132.71, 130.57, 129.50, 128.21, 125.49, 113.24, 70.04, 40.95, 37.52, 30.26, 30.10, 27.30; HRMS for $C_{17}H_{20}O_2$ (M^+) calcd. 256.1463, found 256.1466.

2,2-Dimethyl-6-vinyl-3,4-dihydro-2*H*-pyran-4-yl benzoate (55). To a solution of alcohol **28** (1.14 g, 5 mmol) dissolved in diisopropylethylamine (10 mL) was added benzoyl chloride (2.8 g, 5 mmol). The reaction was stirred overnight with the gradual formation of a white precipitate. Ether was then added to the reaction, which was then washed with saturated sodium bicarbonate and brine, dried and the ether evaporated under reduced pressure, yielding 2.4 g of **55** as a mixture of product, unreacted starting material and unreacted benzoyl chloride. Further purification via flash chromatography yielded 1.4 g (4.21 mmol) **55** as a clear oil. 300 MHz ^{1}H NMR δ 0.95 (3H, t, J = 7 Hz), 1.4 (5H, m), 1.5 (3H, s), 1.6 (2H, quintet, J = 7 Hz), 2.0 (2H, m), 4.2 (2H, J = 7 Hz), 5.6 (1H, m), 6.05 (1H, d, J = 2 Hz), 7.3 (2H, t, J = 8 Hz), 7.6 (1H, t, J = 8 Hz), 7.9 (2H, d, J = 8 Hz); ^{13}C NMR

(75 MHz) δ165.5, 161.9, 145.0, 132.8, 130.2, 129.3, 128.1, 105.6, 75.8, 64.9, 64.3, 37.9, 30.26, 26.62, 25.7, 18.8, 13.4. HRMS for $C_{19}H_{24}O_5$ (M^+) calcd. 332.1623 , found 332.1641.

(Z)-4-(t-butyldimethylsiloxy)but-2-ene-1-ol (56).[87] cis-2-Butene 1,4-diol (6.0 g; 68 mmol) was mixed with diisopropylethyl amine (8.7 g, 68 mmol) in DMF (14 mL). After 20 minutes, TBSCl (10.3 g, 69 mmol) dissolved in DMF (5 mL) was added slowly. The reaction was allowed to stir overnight and then quenched by addition of water (5 mL), followed by the addition of ether (10 mL) and then 5% $NaHCO_3$ (10 mL). The mixture was extracted with ether, the ether layer washed with brine several times to remove the amine, and dried. Evaporation of the solvent afforded 13.80 g of **56**. Flash chromatography yielded 13.15 g (94 %) of pure product as an oil: 300 MHz ^1H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.95 (9H, s), 3.2 (1H, brs), 4.1 (1H, d, J = 8 Hz), 4.2 (1H, d, J = 8 Hz), 5.5 (1H, m), 5.6 (1H, m). ^{13}C NMR (75 MHz) δ130.8, 130.0, 59.5, 25.7, 16.7, -5.4.

(Z)-4-(t-butyldimethylsiloxy)but-2-ene-1-yl benzoate (57). To a solution of **56** (13.0 g, 64 mmol) dissolved in diisopropylethylamine (25 mL) was added benzoyl chloride (9.0 g, 65 mmol). The reaction was stirred overnight

with the gradual formation of a white precipitate. Ether was then added to the reaction, which was then washed with saturated sodium bicarbonate and brine, dried and the ether evaporated under reduced pressure, yielding 19 g of **57** as a mixture of product, unreacted starting material and unreacted benzoyl chloride. Further purification via flash chromatography yielded 12 g (40 mmol) **57** (65% yield) as a clear oil, still containing small amounts of benzoyl chloride. 300 MHz ^{1}H NMR δ 0.05 (6H, s), 0.95 (9H, s), 4.4 (2H, d, J = 6 Hz), 4.9 (2H, d, J = 6 Hz), 5.8 (2H, m), 7.4 (2H, t, J = 8 Hz), 7.8 (1H, t, J = 8 Hz), 8.2 (2H, d, J = 8 Hz); ^{13}C NMR (75 MHz) δ 167.1, 135.9, 132.0, 130.5, 129.5, 128.0, 124.2, 62.1, 60.4, 26.0, 20.6, -5.4.

[(Z)-2-butene-1,4-di-yl]benzoate (59). To a solution of cis-2-butene-1,4-diol (880 mg, 10 mmol) in 5.0M $LiClO_4$ in diethyl ether (5 mL) was added benzoyl chloride (2.8 g, 20 mmol). The solution was stirred at room temperature for 8 hours, diluted with 25 mL diethyl ether and 30 mL water. The ether layer was separated, washed with water and sodium bicarbonate, dried over potassium carbonate, and evaporated under reduced pressure to afford **59** as a yellow oil. Further purification using flash chromatography yielded **59** as a clear oil (2.6 g, 8.7 mmol). 300 MHz ^{1}H NMR δ 5.18 (4H, d, J = 6 Hz), 6.05 (2H, t, J = 6 Hz), 7.5 (4H, t, J = 8 Hz), 7.7 (2H, t, J = 8 Hz), 8.2 (4H, t, J = 8 Hz); ^{13}C NMR

(75 MHz) δ 166.3, 133.0, 129.6, 128.3, 60.5; HRMS for $C_{18}H_{17}O_4$ (M+1) calcd. 297.1126, found 297.1087.

(Z)-4-hydroxybut-2-en-1-yl benzoate (62). To benzoate **57** (1.3 g, 6 mmol) was added a 5.0M solution of lithium perchlorate in diethyl ether (10.0 mL, 50 mmol). The mixture was stirred for 8 hours, turning from clear to bright green. Water was added, followed by ether, the layers were separated and the ether layer washed with saturated sodium bicarbonate, and then brine, dried and evaporated under reduced pressure, resulting in 0.6 g **62** as an oil. Further purification via flash chromatography yielded **62** (0.95 g, 5 mmol) as a yellow liquid (84% yield). 300 MHz ^1H NMR δ 2.2 (1H, brs), 4.4 (2H, d, J = 8 Hz), 4.95 (2H, d, J = 8 Hz), 5.8 (1H, m), 5.95 (1H, m), 7.4 (2H, t, J = 8 Hz), 7.6 (1H, t, J = 8 Hz), 8.05 (d, J = 8 Hz) ^{13}C NMR (75 MHz) δ 166.6, 133.5, 133.0, 129.6, 128.3, 125.5, 60.6, 58.4. HRMS for $C_{11}H_{12}O_3$ (M^+) calcd. 192.0786, found 192.0779.

Butyl 2,2-dimethylpyran-6-carboxylate (63). To silyl ether **29** (230 mg, 1 mmol) was added a 5.0M solution of lithium perchlorate in diethyl ether (3.0 mL, 15 mmol). The mixture was stirred for 80 hours, turning from clear to yellow. Water was added, followed by ether, the layers were separated and the ether layer washed with saturated sodium

bicarbonate, and then brine, dried and evaporated under reduced pressure, resulting in 190 mg **63** as an oil. Further purification via flash chromatography yielded **63** (170 mg, 0.8 mmol) as a clear liquid. 300 MHz ^{1}H NMR δ 0.95 (3H, t, J = 7 Hz), 1.4 (8H, brs), 1.6 (4H, m), 4.2 (2H, t, J = 7 Hz), 5.4 (1H, d, J = 13 Hz), 5.9 (1H, dd, J = 7 Hz, J = 13 Hz), 6.2 (1H, d, J = 7 Hz); ^{13}C NMR (75 MHz) δ 163.12, 130.15, 124.78, 119.63, 108.176, 76.58, 64.80, 30.56, 26.86, 19.06, 14.64; HRMS for $C_{12}H_{19}O_3$ (M+1) calcd. 211.1334, found 211.1349.

(4-t-butyl)-carbethoxymethylidinecyclohexane (64).[88] To a solution of hexamethyldisilazane (0.8 mL, 2 mmol) in THF (20 mL) cooled to -78°C was added a 2.5 M solution of nBuLi (0.5 mL, 2 mmol). The solution was allowed to warm to -40°C, and triethylphosphonoacetate (450 mg, 2 mmol) was added. After 15 minutes, a solution of 4-t-butylcyclohexanone (310 mg, 2 mmol) in THF (10 mL) was added. The mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction was transferred into a separatory funnel and 50 mL of water were added. The organic layer was separated, washed with brine, while the aqueous layer was extracted with methylene chloride. The combined organic layers were dried and the solvent removed under reduced pressure, affording **64** as a crude mixture. Further purification via flash chromatography yielded **64** as a clear oil (320 mg, 1.5 mmol) (75% yield). 300 MHz ^{1}H NMR ($CDCl_3$) δ

0.76 (9H, s), 1.2 (3H, t, J = 7 Hz), 1.4 (1H, m), 1.7-2.4 (8H, m), 4.0 (2H, q, J = 7 Hz), 5.5 (1H, s); ^{13}C NMR (75 MHz) δ 167.1, 163.2, 112.6, 59.3, 47.7, 41.2, 37.7, 29.4, 29.0, 28.3, 27.4, 14.2; HRMS for $C_{14}H_{24}O_2$ (M+1) calcd. 225.1776, found 225.1785.

1-(2-hydroxyethylidine)-4-t-butylcyclohexane (65).[89] To a solution of ester **64** (450 mg, 2 mmol) in THF (50 mL) cooled to -78°C was added a 1.0 M DIBAL solution in hexanes (4.4 mL, 2.2 mmol). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with methanol (1 mL) and poured onto 100 mL of saturated sodium potassium tartrate solution, followed by vigorous stirring for 5 hours. The layers were separated and the organic layer was washed with small portions of brine, dried over magnesium sulfate and anhydrous potassium carbonate. Removal of the solvent under reduced pressure yielded **65** (345 mg, 1.9 mmol) as a yellow oil. Further purification using flash chromatography was carried out, affording 325 mg (1.8 mmol) of pure **65** as a clear oil (85% yield). 300 MHz ^1H NMR ($CDCl_3$) δ 0.8 (9H, s), 1.0-2.3 (6H, m), 2.6 (2H, d, J = 10 Hz), 4.1 (2H, d, J = 7 Hz), 5.3 (1H, t, J = 7 Hz); ^{13}C NMR (75 MHz) δ 143.6, 120.0, 58.2, 48.1, 36.8, 28.9, 28.5, 28.3, 27.4, 25.5.

1-(2-benzoyloxyethylidine)-4-t-butylcyclohexane (66). To a solution of **65** (365 mg, 2 mmol) dissolved in diisopropylethylamine (5 mL) was added benzoyl chloride (280 mg, 2 mmol). The reaction was stirred overnight with the gradual formation of a white precipitate. Ether was then added to the reaction, which was then washed with saturated sodium bicarbonate and brine, dried and the ether evaporated under reduced pressure, yielding 480 mg of **66** as a mixture of products, including unreacted starting material and unreacted benzoyl chloride. Further purification via flash chromatography yielded 400 mg (1.4 mmol) **66** as a clear oil (70%). 300 MHz ^{1}H NMR δ 0.95 (9H, s), 1.0-1.4 (4H, m), 1.8-2.0 (3H, m), 2.05 (1H, m), 2.35 (1H, d, J = 10 Hz), 2.8 (1H, d, J = 10 Hz), 4.8 (2H, d, J = 7 Hz), 5.4 (1H, t, J = 7 Hz), 7.4 (2H, t, J = 8 Hz), 7.6 (1H, t, J = 8 Hz), 8.05 (2H, d, J = 8 Hz); ^{13}C NMR (75 MHz) δ 166.5, 146.7, 132.6, 130.5, 129.5, 128.2, 114.9, 61.2, 48.1, 36.8, 32.4, 28.9, 28.8, 28.3, 27.5. HRMS for $C_{19}H_{25}O_2$ (M^+) calcd. 285.1854, found 285.1959.

1-phenyl-1-pentanol (67).[90] To a solution of benzaldehyde (30 g, 280 mmol), in THF (250 mL) cooled to -78°C was added a 1.6M solution of nBuLi in hexanes (180 mL, 280 mmol). The solution was allowed to warm to room temperature overnight, and then quenched with methanol (5 m).

The mixture was diluted with ether (300 mL), extracted with brine, the ether layer dried over magnesium sulfate and evaporated to afford **67** (44 g). Purification via flash chromatography yielded 38 g (231 mmol) **67** as a yellow oil. 300 MHz ^{1}H NMR δ 0.95 (3H, t, J = 7 Hz), 1.4 (4H, m), 1.8 (2H, m), 2.4 (1H, brs), 4.6 (1H, t, J = 7 Hz), 7.4 (5H, brs); ^{13}C NMR (75 MHz) δ 144.94, 128.26, 127.29, 125.83, 74.50, 38.73, 27.89, 22.52, 13.91. HRMS for $C_{11}H_{16}O$ (M^{+}) calcd. 164.1201, found 164.1212.

1-(t-butyldimethylsilyloxy)-1-phenylpentane (68). Benzylic alcohol **67** (5 g, 30 mmol) was mixed with diisopropylethyl amine (3.8 g, 30 mmol) in DMF (7 mL) . After 20 minutes, TBSCl (4.35 g, 30 mmol) dissolved in DMF (2 mL) was added slowly. The reaction was allowed to stir overnight and then quenched by addition of water (5 mL), followed by the addition of ether (10 mL) and then 5% $NaHCO_3$ (10 mL). The mixture was extracted with ether, the ether layer washed with brine several times to remove the amine, and dried. Evaporation of the solvent afforded 8.0 g of **68**. Flash chromatography yielded 7.6 g (90 %) of pure product as an oil: 300 MHz ^{1}H NMR ($CDCl_3$) d -0.05 (3H, s), 0.05 (3H, s), 0.95 (12H, brs), 1.4 (4H, m), 1.8 (2H, m), 4.75 (1H, m), 7.4 (5H, brs); ^{13}C NMR (75 MHz) δ 146.0, 127.98, 126.77, 125.92, 75.17, 40.80, 27.87, 25.93, 25.76, 25.70, 14.1, -4.55, -4.90. HRMS for $C_{17}H_{30}SiO$ (M+1) calcd. 279.2065, found 279.2088.

(R)-2-t-Butyldimethylsilyoxyoctane (69). (R)-2-Octanol (250 mg, 1.9 mmol) was mixed with diisopropylethyl amine (250 mg, 2 mmol) in DMF (0.5 mL) . After 20 minutes, TBSCl (300 mg, 2 mmol) dissolved in DMF (0.3 mL) was added slowly. The reaction was allowed to stir overnight and then quenched by addition of water (1 mL), followed by the addition of ether (3 mL) and then 5% $NaHCO_3$ (3 mL). The mixture was extracted with ether, the ether layer washed with brine several times to remove the amine, and dried. Evaporation of the solvent afforded 500 mg of **69**. Flash chromatography yielded 420 mg (90 %) of pure product as an oil: 300 MHz ^1H NMR ($CDCl_3$) δ 0.1 (6H, s), 0.9 (9H, s), 1.2 (3H, d, J = 6 Hz), 1.3 (13H, m), 3.8 (1H, m); ^{13}C NMR (75 MHz) δ 68.7, 39.8, 31.9, 29.4, 25.9, 23.8, 22.7, 18.2, 14.1, -4.3, -4.7. HRMS for $C_{14}H_{32}SiO$ (M+1) calcd. 245.2222, found 245.2236.

Lithium Perchlorate Deprotection of 69: To silyl ether **69** (2.4 g, 10 mmol) was added a 5.0M solution of lithium perchlorate in diethyl ether (10.0 mL, 50 mmol). The mixture was stirred for 120 hours at room temperature. Water was added, followed by ether, the layers were separated and the ether layer washed with saturated sodium bicarbonate, and then brine, dried and evaporated under reduced pressure,

resulting in 2.2 g of a crude mixture. NMR data confirmed that the mixture contained 2-octanol, unreacted **69**, and TBSOH. The integration of the α-methine protons of the alcohol and of **69** revealed a 1:5 ratio of product to starting material. Further purification via flash chromatography enabled the separation of the mixture and afforded 190 mg of 2-octanol along with 1.6 g of recovered **69**. Optical activity measurements for the recovered 2-octanol afforded $[\alpha]^{23}_{D}$ = 0.2° (c=0.01), consistent with the proposed racemization. The recovered **69** was subjected to deprotection using a 1.0 M solution of tetrabutyl ammonium fluoride (8 mL, 8 mmol) in THF, affording 2-octanol as an oil. Purification via flash chromatography afforded a pure sample of 2-octanol (750 mg, 5.8 mmol). Optical rotation measurements found $[\alpha]^{23}_{D}$ = -4.1° (c=0.01), indicating approximately 50% racemization.

2,2-dimethyl-6-[2-(E)-carbethoxyvinyl]-4-(hydroxy)-3,4-dihydro-2*H*-pyran (70). To a solution of **44** (680 mg, 2 mmol) was added a 1.0M solution of tetrabutylammonium fluoride in THF (2 mL, 1 mmol). The resulting mixture was stirred overnight at room temperature, with the color changing from yellow to brown. The reaction was quenched with water, the layers were separated, the organic layer washed with brine, dried over magnesium sulfate and evaporated, yielding **70** as a crude oil containing t-butyldimethylsilyl alcohol. The mixture was separated using

flash chromatography, resulting in a clear oil **70** (271 mg, 1.2 mmol). 300 MHz ^{1}H NMR δ 1.2 (3H, s), 1.25 (3H, t, J = 7 Hz), 1.3 (3H, s), 2.95 (1H, brs), 4.2 (2H, q, J = 7 Hz), 4.4 (1H, m), 5.2 (1H, d, J = 2 Hz), 6.2 (1H, d, J = 15 Hz), 6.95 (1H, d, J = 15 Hz); ^{13}C NMR (75 MHz) δ 167.0, 148.5, 139.9, 118.5, 11.0, 75.6, 61.9, 60.3, 41.9, 28.0, 25.1, 14.1. HRMS for $C_{12}H_{18}O_4$ calcd. 226.1205, found 226.1206.

APPENDIX
TABLES OF CRYSTALLOGRAPHIC DATA

Supplementary Table 1: Crystallographic data for **20**.

A. Crystal data (298 K)	**1**
a, Å	8.649(1)
b, Å	10.794(1)
c, Å	15.936(2)
V, Å^3	1484.6(7)
d_{calc}, g cm^{-3}(298 K)	1.227
Empirical formula	$C_{17}H_{22}O_3$
Formula wt, g	274.35
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
Z	4
F(000), electrons	592
Crystal size (mm^3)	0.49 x 0.42 x 0.17
B. Data collection (298 K)	
Radiation, l (Å)	Mo-K_a, 0.71073
Mode	w-scan
Scan range	Symmetrically over 1.2∞ about
maximum	
Background	offset 1.0 and -1.0 in w from
maximum	
Scan rate, deg. min.$^{-1}$	3 – 6
2q range, deg.	3 – 50
Range of *h k l*	$0 \leq h \leq 11$
	$0 \leq k \leq 14$
	$0 \leq l \leq 20$
Total reflections measured	1982
Unique reflections	1960
Absorption coeff. m (Mo-K_a), mm^{-1}	0.08
Min. & Max. Transmission	0.964 0.986
C. Structure refinement	
S, Goodness-of-fit	1.62
Reflections used, I > 2s(I)	1517
No. of variables	269
R, wR* (%)	5.16, 5.3
$R_{int.}$ (%)	0.0000
Max. shift/esd	0.001

Supplementary Table 1 continued.

min. peak in diff. four. map (e $Å^{-3}$) -0.2
max. peak in diff. four. map (e $Å^{-3}$) 0.2

* Relevant expressions are as follows, where in the footnote F_o and F_c represent, respectively, the observed and calculated structure-factor amplitudes.
Function minimized was $w(|F_o| - |F_c|)^2$, where $w = (s(F))^{-2}$
$R = Å(||F_o| - |F_c||) / Å|F_o|$
$wR = [Åw(|F_o| - |F_c|)^2 / Å |F_o|^2]^{1/2}$
$S = [Åw(|F_o| - |F_c|)^2 / (m-n)]^{1/2}$

Suppelementary Table 2: Fractional coordinates and isotropic thermal parameters ($Å^2$) for the H atoms of compound **20**

Atom	x	y	z	U
H2a	0.834(4)	0.314(2)	0.475(2)	0.023(7)
H5	0.404(4)	0.532(3)	0.525(2)	0.039(9)
H7a	0.448(5)	0.463(4)	0.289(2)	0.063(11)
H7b	0.474(4)	0.592(3)	0.247(2)	0.050(10)
H8a	0.685(5)	0.440(4)	0.213(2)	0.067(11)
H8b	0.739(4)	0.564(4)	0.265(2)	0.054(11)
H8c	0.858(5)	0.394(3)	0.326(2)	0.059(11)
H9a	0.871(5)	0.615(4)	0.416(3)	0.071(13)
H9b	0.958(5)	0.503(3)	0.446(2)	0.066(12)
H9c	0.845(6)	0.574(4)	0.512(3)	0.10(2)
H10a	0.703(6)	0.244(5)	0.679(3)	0.10(2)
H10b	0.819(7)	0.235(5)	0.620(3)	0.11(2)
H10c	0.700(8)	0.156(7)	0.608(4)	0.15(3)
H12a	0.308(6)	0.526(5)	0.661(3)	0.09(2)
H12b	0.452(6)	0.613(4)	0.667(3)	0.10(2)
H12c	0.373(5)	0.534(4)	0.747(3)	0.078(13)
H13a	0.266(5)	0.561(4)	0.400(2)	0.055(11)
H13b	0.293(6)	0.683(5)	0.340(3)	0.09(2)
H13c	0.315(5)	0.679(4)	0.442(3)	0.065(12)
H14a	0.693(5)	0.722(3)	0.353(2)	0.056(11)
H14b	0.533(6)	0.783(4)	0.332(3)	0.09(2)
H14c	0.576(5)	0.765(4)	0.425(3)	0.080(15)

Supplementary Table 3: Bond Lengths (Å) and Angles (°) of the H atoms of compound **20**.

1	2	3	1-2	1-2-3
H2a	C2a	C3	0.91(3)	110.(2)
H2a	C2a	C8b		107.(2)
H2a	C2a	C2		103.(2)
H5	C5	C8c	0.89(3)	121.(2)
H5	C5	C4		114.(2)
H7a	C7	H7b	0.97(4)	108.(3)
H7a	C7	C8		107.(2)
H7b	C7	C8	0.96(4)	111.(2)
H7b	C7	C6		107.(2)
H8a	C8	H8b	1.07(4)	109.(3)
H8a	C8	C8a		104.(2)
H8a	C8	C7		115.(2)
H8b	C8	C8a	0.94(4)	106.(2)
H8b	C8	C7		109.(2)
H8c	C8a	C8b	1.04(4)	108.(2)
H8c	C8a	O1		107.(2)
H8c	C8a	C8		113.(2)
H9a	C9	H9b	0.94(4)	103.(3)
H9a	C9	H9c		111.(4)
H9a	C9	C8b		113.(2)
H9b	C9	H9c	0.98(4)	110.(4)
H9b	C9	C8b		110.(2)
H9c	C9	C8b	1.00(5)	109.(3)
H10a	C10	H10b	1.02(6)	102.(5)
H10a	C10	H10c		100.(5)
H10a	C10	C3		115.(3)
H10b	C10	H10c	0.75(6)	108.(6)
H10b	C10	C3		115.(4)
H10c	C10	C3	0.91(8)	115.(4)
H12a	C12	H12b	0.87(5)	110.(5)
H12a	C12	H12c		107.(4)
H12a	C12	C11		100.(3)
H12b	C12	H12c	1.02(5)	114.(4)
H12b	C12	C11		114.(3)
H12c	C12	C11	0.96(5)	110.(3)
H13a	C13	H13b	0.96(4)	114.(4)
H13a	C13	H13c		101.(3)
H13a	C13	C6		113.(2)
H13b	C13	H13c	1.00(5)	112.(4)
H13b	C13	C6		106.(3)
H13c	C13	C6	0.98(4)	111.(2)
H14a	C14	H14b	0.99(4)	109.(4)
H14a	C14	H14c		109.(3)
H14a	C14	C6		113.(2)
H14b	C14	H14c	0.94(5)	108.(4)
H14b	C14	C6		111.(3)
H14c	C14	C6	0.97(4)	106.(3)

Supplementary Table 4. Crystal data and structure refinement for **35**.

Empirical formula	C28 H56 O6 Si2
Formula weight	544.91
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.6560(3) A a = 90° b = 12.9003(3) A b = 108.428(1)° c = 10.7718(1) A g = 90°
Volume, Z	1668.49(6) A^3, 2
Density (calculated)	1.085 Mg/m^3
Absorption coefficient	0.140 mm^-1
F(000)	600
Crystal size	0.26 x 0.22 x 0.07 mm
Theta range for data collection	1.70 to 27.50 deg.
Limiting indices	-14<=h<=16, -17<=k<=9, -14<=l<=13
Reflections collected	11397
Independent reflections	3822 [R(int) = 0.0358]
Absorption correction	Psi scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3779 / 0 / 255
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0487, wR2 = 0.1022 [2702]
R indices (all data)	R1 = 0.0812, wR2 = 0.1312
Extinction coefficient	0.0036(9)
Largest diff. peak and hole	0.251 and -0.179 e.A^-3

Supplementary Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **35**

	x	y	z	U(eq)
H3A	7233(18)	-1508(16)	6263(21)	34(5)
H3B	7848(21)	-1618(19)	7753(26)	62(7)
H4	8507(18)	100(16)	7758(22)	36(6)
H5A	7379(18)	123(16)	5000(21)	36(6)
H5B	8204(19)	1018(19)	5785(22)	49(7)
H7A	8360(17)	-317(16)	3414(20)	31(5)
H7B	8857(17)	768(17)	3881(20)	36(6)
H9A	8011(27)	-2912(23)	5412(31)	84
H9B	9359(26)	-3206(23)	6057(30)	84
H9C	8625(25)	-3284(24)	7008(30)	84
H10A	10111(24)	-922(23)	8209(28)	78
H10B	10619(25)	-1978(22)	7677(28)	78
H10C	9842(24)	-2117(23)	8560(29)	78
H12A	7142(27)	770(25)	10509(32)	90
H12B	8031(29)	287(25)	9991(32)	90
H12C	6890(27)	-321(26)	9845(31)	90
H13A	8144(38)	2177(33)	8462(41)	135
H13B	7042(36)	2533(32)	7196(45)	135
H13C	7139(35)	2696(33)	8787(41)	135
H15A	4957(27)	2282(27)	6490(32)	92
H15B	4836(27)	1233(25)	5777(32)	92
H15C	3767(28)	1653(25)	6141(31)	92
H16A	4957(24)	-375(23)	8562(30)	77
H16B	4784(24)	-442(23)	6954(29)	77
H16C	3796(26)	26(21)	7461(28)	77
H17A	5150(26)	1383(24)	9685(32)	89
H17B	3997(28)	1773(24)	8498(30)	89
H17C	5149(26)	2428(26)	8888(31)	89

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BIOGRAPHICAL SKETCH

Lucian Boldea was born in 1971 in Arad, Romania. The son of a chemist and an engineer, he was exposed to sciences from a very young age. After graduating from High School, he moved to the United States and studied chemistry at the University of West Florida. Under the patient guidance of Dr. R. K. Birdwhistell, Lucian decided to pursue a career in research chemistry. He received his B.S. degree from the University of West Florida in 1992 and was admitted to graduate school at the University of Florida beginning in the Fall of 1992. While his initial intentions were to pursue a career in organometallic chemistry, participation in mechanistic and synthetic Bull Sessions during his first semester sparked his interest for organic chemistry.

In the spring of 1993 he joined the research group of Professor Merle A. Battiste and started work in the area of total synthesis of natural products. Upon graduation, Lucian will take a position as an Advanced Process Scientist with Eastman Chemical in Kingsport, Tennessee.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste, Chair
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier Jr.
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

J. Eric Enholm
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Nigel G. J. Richards
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 1997

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Dean, Graduate School